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EXPLAINABLE ENSEMBLE MACHINE LEARNING FRAMEWORK FOR PREDICTING DRUG RELEASE BEHAVIOR IN POLYMERIC LONG-ACTING INJECTABLE SYSTEMS

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ABSTRACT

Predicting drug release from polymeric long-acting injectable systems remains challenging because release behavior depends on nonlinear interactions among formulation, physicochemical, and temporal variables. This study developed an explainable ensemble machine learning framework for predicting drug release behavior and identifying the most influential release-governing variables. A secondary experimental dataset containing 3,783 observations and 20 variables was analyzed. Data preprocessing included quality inspection, categorical encoding, exclusion of identifier variables, and train-test splitting. Linear Regression, Random Forest, and XGBoost models were developed and evaluated using R^2, mean absolute error, and root mean square error. Feature importance and residual analyses were additionally performed to assess interpretability and model reliability. XGBoost achieved the best predictive performance with an R^2 of 0.9849, MAE of 0.0276, and RMSE of 0.0406, outperforming Random Forest and Linear Regression. The strongest predictors were T = 1.0, Drug NHA, SE, Drug Mw, and Time. Residual analysis demonstrated low prediction bias and stable error distribution, supporting the robustness of the optimized model. The findings indicate that explainable ensemble learning can accurately model complex release behavior in polymeric long-acting injectable systems and may support efficient formulation screening, optimization, and data-driven pharmaceutical engineering.

1. Introduction

The development of controlled drug delivery systems has revolutionized modern medicine in many ways because they improve the bioavailability of the drug, decrease the dose frequency, and increase patient compliance. The systems help to achieve sustained and targeted drug delivery, while also reducing the fluctuations in plasma drug levels and minimising systemic side effects (Ezike et al., 2023). Long-acting injectable formulations (LAIFs) are one of the several strategies that have evolved in sustained therapeutics as they offer continuous drug release over a long duration and better adherence towards treatment for the management of chronic diseases. With the rising need for patient-friendly and efficient therapeutic systems, the research into biodegradable polymer-based drug delivery technologies (Adepu & Ramakrishna, 2021) has increased. Biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL) and polylactic acid (PLA) are commonly used for long-acting injectables due to their excellent biocompatibility and controllable degradation. These materials can control the diffusion of drugs, the erosion of the matrix and the sustained release rate kinetics, which can make them suitable for controlled drug therapeutic applications (Muddineti & Omri, 2022). Because of their effectiveness in anticancer therapeutics and long-term drug delivery, the development of PCL-, PLA-, and PLGA-based delivery technologies has become more meaningful and important in the advanced pharmaceutical design, as recently demonstrated (Kim et al., 2025). Even with these developments, the prediction of drug release behaviour from polymeric systems is still a real challenge since several variables are involved and interconnected in governing the release kinetics. Degradation and diffusion mechanisms are a combination of polymer composition, molecular weight, surface morphology, drug solubility and formulation ratios. Proteins, peptides, and hydrophilic compounds can be especially tricky in long-acting formulations due to potential issues like burst release, diffusion dependent on degradation, and varying encapsulation efficiencies (Nakmode et al., 2025). Hence, the optimization of these systems through experiments must be performed, which means more laboratory testing, a higher development time and costs. Traditional kinetic and mathematical models have been abundantly used to describe release mechanisms and stability behavior for controlled drug delivery systems. These models are important as they give theoretical insight into degradation, diffusion and dissolution phenomena of pharmaceutical formulations (Rehman et al., 2020). In the same fashion, kinetic models are also applied to describe drug release profiles and elucidate the release mechanism in a polymeric matrix under various physiological conditions (Askarizadeh et al., 2023). Other mechanistic models, however, do not necessarily reflect the nonlinear relationships of several formulation descriptors and dynamic release variables, especially in complex biodegradable polymer systems. Experimental studies have also revealed a strong influence of polymer architecture and polymer structure on the long-term release performance. For long-term release systems, the diffusion and matrix degradation have been reported to happen simultaneously in controlled release systems using electrospun polymeric fibres, leading to extremely coupled release behavior (Wu et al., 2020). Furthermore, computational research involving molecular dynamics simulations has revealed the importance of intermolecular interactions, polymer architecture, and diffusion behaviour in polyester-based long-acting injectable systems (Kotla et al., 2023). These findings suggest that release kinetics are due to a multidimensional interaction that cannot be fully described by conventional approaches to predict release. In recent times, AI and ML have appeared as potential instruments to address pharmaceutical formulation design and drug delivery optimization. These algorithms are capable of handling vast and varied datasets, uncovering complex patterns and relationships between variables, and constructing predictive models with high precision, all of which are valuable in the field of pharmaceuticals (Vora et al., 2023). AI's role in drug discovery and drug delivery studies has also led to the advancement of personalized medicine and data-driven therapeutic solutions (Serrano et al., 2024). Recent studies have also shown that machine learning models can be used to speed up the optimization of polymeric long-acting injectable formulations by accurately modelling the complex relationships between formulation descriptors and the release behaviour (Bannigan et al., 2022). With the rise of computational pharmaceutical engineering, long-acting injectables (LAI) are not just for traditional therapeutic applications, but are important in veterinary medicine and sustained biologic delivery,

where long-acting therapeutic effects are crucial (Koppisetti et al., 2025). However, few works have been dedicated to explainable ensemble machine learning models that can also offer both high predictive accuracy and explainable analysis of the major variables that affect release kinetics in biodegradable polymer systems. This work thus builds an explainable ensemble machine learning system to predict drug release behavior of polymeric long-acting injectable systems. Several machine learning models using multiple regression are evaluated, and the effects of physicochemical, formulation-related and temporal variables are explored in the context of release prediction. Combining predictive modelling, feature importance and residual analysis, the study aims to develop an interpretable computational tool that can help to efficiently optimize the formulation for effective drug delivery while also promoting data-driven pharmaceutical engineering research.

2. Methodology

2.1 Research Design

This study used a quantitative research approach using supervised machine learning techniques to predict behaviour of drug release in polymeric long-acting injectable formulation. Secondary experimental data consisting of physicochemical descriptors, formulation parameters, and temporal release characteristics were used for the development of predictive regression models. The methodological approach focused on assessing the predictive performance of different machine learning algorithms and identifying the variables influencing release kinetics. A computational modelling approach was used in which the formulation-related variables were considered as the predictive variables and the cumulative drug release was considered as the target variable. The accuracy and reliability of the model were measured in terms of the regression evaluation metrics.

2.2 Data Source

The data used in this study came from the study by Bannigan et al. (2022), who explored machine learning methods to facilitate the design of polymeric long-acting injectables. The data set comprised experimental formulation and drug-related descriptors associated with drug release behaviour in a biodegradable polymer system. The variables that were collected were variables on polymer properties, molecular descriptors, formulation ratios, and engineered temporal release variables relevant to long-acting injectable formulations. There were 20 variables and 3,783 observations in the dataset. There were two versions of the data set: a 14-feature version and a 17-feature version. The 17-feature data set was used in the present study since it contained further engineered temporal features that had a higher predictive power.

2.3 Data Preprocessing

Data preprocessing was done to ensure data quality and consistency for analysis before developing the data model. The data was initially checked for missing values, duplicate data and inconsistencies in the data. During the pre-processing stage, no missing values or duplicate records were found. The categorical formulation variable is converted into a numerical variable, using label encoding, to make it compatible with machine learning algorithms. To avoid information leakage and overestimate the predictive performance, the identifier variable of experimental indexing was not used in modeling. The data set was then split into the predictor variables and the target variable. The release of the drug was chosen as the dependent variable, while all the other formulation, physicochemical and time variables were considered to be independent.

2.4 Feature Scaling and Data Splitting

The data was split into training and test data with an 80-20 ratio. Model learning was performed with the training subset, while an independent performance evaluation was done with the testing subset. A fixed random state has been used in splitting to ensure that the experimental procedure could be reproduced. Standardization of features was implemented using standard scaling techniques, which involved normalizing the distribution of the features and enhancing the numerical stability during the

model training process. As tree-based algorithms are not generally sensitive to feature scaling, the original values of the features were used in the ensemble-based models.

2.5 Exploratory Data Analysis

Exploratory data analysis (EDA) was used to explore data and to investigate the statistical properties and relationships between variables. For all continuous variables, the mean, standard deviation, minimum, maximum and quartile distribution of values were calculated. Correlation analysis was also conducted for the linear association between the formulation parameters and release behavior. To understand the inter-variable relationship and to see if there are any possible dependencies among the physicochemical and the engineered temporal variables, a correlation heatmap was created.

2.6 Machine Learning Model Development

Three regression algorithms were used: Linear Regression, Random Forest and Extreme Gradient Boosting (XGBoost). Linear Regression was used as a baseline statistical model for the assessment of conventional linear approaches for the prediction of release behaviour. Two classifiers, namely Random Forest (RF) and XGBoost (XG), were chosen because they can capture complex relationships and interactions between formulation variables. Random Forest adopted the idea of ensemble learning (multiple decision trees), and XGBoost applied gradient boosting optimization to minimize the predictive error of the model. We trained the model with the training dataset and made predictions with the testing dataset to assess the generalization performance of the model.

2.7 Model Evaluation

The coefficient of determination (R^2), mean absolute error (MAE) and root mean square error (RMSE) were used to evaluate the performance of the models. The percentage of variance explained by the model was calculated using the R^2 value, while the magnitude of prediction error was calculated by using the MAE and RMSE. A comparative evaluation of the three types of regression models was performed to choose the most exact predictive model for modeling the drug release behavior.

2.8 Feature Importance and Residual Analysis

To identify the relative influence of the predictor variables on release prediction, the optimized XGBoost model was used for feature importance analysis. Importance scores were directly taken from the trained model and ranked to determine which are the most significant formulation and molecular descriptors. The model reliability and the possible systematic prediction errors were also examined using residual analysis. Residual plots and residual distribution analysis were created to examine the stability of the predictions, symmetry of the distribution of the residuals, and the overall robustness of the model.

3. Results

3.1 Descriptive Characteristics of the Dataset

The secondary data comprised 3783 observations and continuous variables related to polymer properties, physicochemical descriptors, formulation parameters and temporal release characteristics. There was no missing value or duplicate record found during the preprocessing. The descriptive statistics showed significant variability in the number of variables related to the formulation, such as polymer MW, surface area to volume ratio (SA-V), and drug MW, thus showing high variability within the data set. The descriptive statistics of continuous variables included in the analysis are shown in Table 1. Average release value was 0.4649 ± 0.3289, indicating that there was a wide range of release behavior of the formulations investigated. The distributions were also wide for the time-related variables, indicating large temporal differences in the release kinetics of polymer-drug systems.

Table 1. Descriptive Statistics of Continuous Formulation and Drug Release Variables

Variable	Mean	Standard Deviation	Minimum	Maximum
LA/GA	0.8047	1.0146	0.0000	3.0000
Polymer MW	35788.2435	24367.6968	8300.0000	108000.0000
CL Ratio	0.0629	0.0674	0.0000	0.1800
Drug Tm	212.5016	66.1702	66.0000	312.5000
Drug Pka	10.7064	2.5326	4.4000	19.6900
Initial D/M ratio	0.7064	0.6265	0.0062	2.5000
DLC	0.1853	0.1292	0.0041	0.6190
SA-V	696.8903	2298.2166	2.4848	22018.3486
SE	0.2926	0.2610	0.0000	1.0000
Drug Mw	568.6651	279.7550	130.0780	1269.4730
Drug TPSA	143.0504	85.8831	23.4700	466.3400
Drug NHA	9.9701	5.4941	2.0000	30.0000
Drug LogP	2.9065	1.5345	-2.2131	5.8465
Time	25.2821	33.3936	0.0000	190.0000
T = 0.25	0.0515	0.0527	0.0013	0.3149
T = 0.5	0.0854	0.0816	0.0040	0.4886
T = 1.0	0.1365	0.1256	0.0055	0.7184
Release	0.4649	0.3289	0.0000	1.0675

3.2 Correlation Analysis of Formulation Variables

To explore the possibility of linear relationships between physicochemical descriptors, formulation variables and release characteristics, correlation analysis was performed. Moderate to strong relationships were found between molecular descriptors and constructed temporal variables. Good positive relationships were found between Drug Mw, Drug TPSA and Drug NHA, suggesting that the three molecular properties together might be contributing to diffusion and release. Figure 1 shows the correlation heatmap between the variables of the data set. Results showed that Time had the highest positive association (r = 0.49) and LA/GA had a moderate negative association (r = -0.24). Furthermore, high correlation was found between engineered temporal variables, especially between period T = 0.5 and period T = 1.0, indicating high interdependence of time-derived variables.

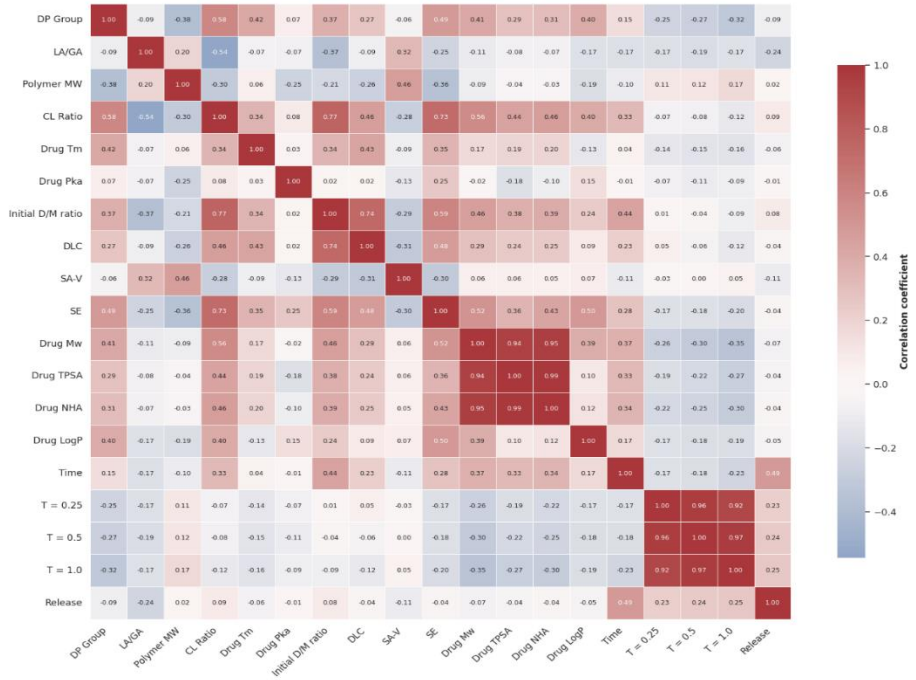

Figure 1. Correlation Heatmap of Formulation and Drug Release Variables

3.3 Comparative Performance of Regression Models

The three algorithms, namely Linear Regression, Random Forest and XGBoost, were tested for the prediction of drug release behavior. This ensemble-based learning model achieved significant improvement over the conventional linear approach on all evaluation measures. Comparative performance of the investigated regression models is given in Table 2. XGBoost had the best predictive output with an R2 score of 0.9849, a mean absolute error of 0.0276 and a root mean square error of 0.0406. Random Forest was also able to predict very well with an R2 value of 0.9821. Linear Regression, on the other hand, achieved significantly poorer accuracy ($R^2 = 0.4534$), demonstrating that this relationship is highly nonlinear.

Table 2. Comparative Performance of Machine Learning Regression Models

Regression Model	R^2 Score	Mean Absolute Error	Root Mean Square Error
XGBoost	0.9849	0.0276	0.0406
Random Forest	0.9821	0.0293	0.0443
Linear Regression	0.4534	0.1984	0.2447

3.4 Prediction Accuracy of the Optimized Model

The actual vs. predicted regression analysis was also undertaken to test the predictive ability of the optimized XGBoost algorithm. Most of the data points were near the ideal line of prediction, and there was high consistency between the actual and predicted release values. The actual vs. predicted release values determined using the optimized XGBoost algorithm are illustrated in Figure 2. The deviation of most of the data points from the line of reference (diagonal line) was minimal, reflecting the high predictive ability and generalization capacity of the optimized XGBoost model. There was a minor dispersion in the extreme release values of the data points.

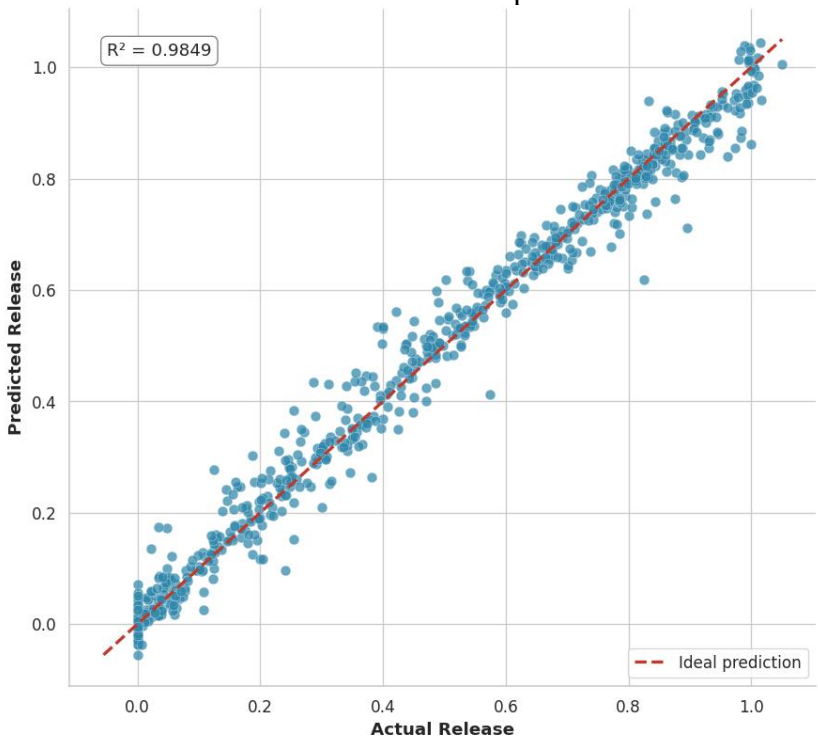

Figure 2. Actual Versus Predicted Drug Release Values Using the XGBoost Model

3.5 Feature Importance Analysis

The improved version of XGBoost was used for the feature selection process to get important features that affect the release behavior. The temporal and molecular attributes were observed to be important factors. Below is Table 3 showing the feature importance rankings based on the scores obtained using

the XGBoost algorithm. In the table below, the temporal feature T = 1.0 had the highest importance score (0.1840), followed by the Drug NHA, SE, Drug Mw, and Time features.

Table 3. Feature Importance Rankings Derived from the XGBoost Model

Rank	Predictor Variable	Importance Score
1	T = 1.0	0.1840
2	Drug NHA	0.1384
3	SE	0.1282
4	Drug Mw	0.1273
5	Time	0.1234
6	Drug TPSA	0.0628
7	CL Ratio	0.0320
8	Polymer MW	0.0283
9	Drug Tm	0.0254
10	Initial D/M ratio	0.0252
11	Drug Pka	0.0231
12	SA-V	0.0189
13	LA/GA	0.0153
14	T = 0.5	0.0153
15	Drug LogP	0.0145
16	DP Group	0.0141
17	T = 0.25	0.0129
18	DLC	0.0108

Figure 3 shows the graph of the scores of the importance of the features of the XGBoost model. The visualization confirms that engineered temporal variables and molecular descriptors are the main parameters that define the release behavior for the different polymer systems investigated.

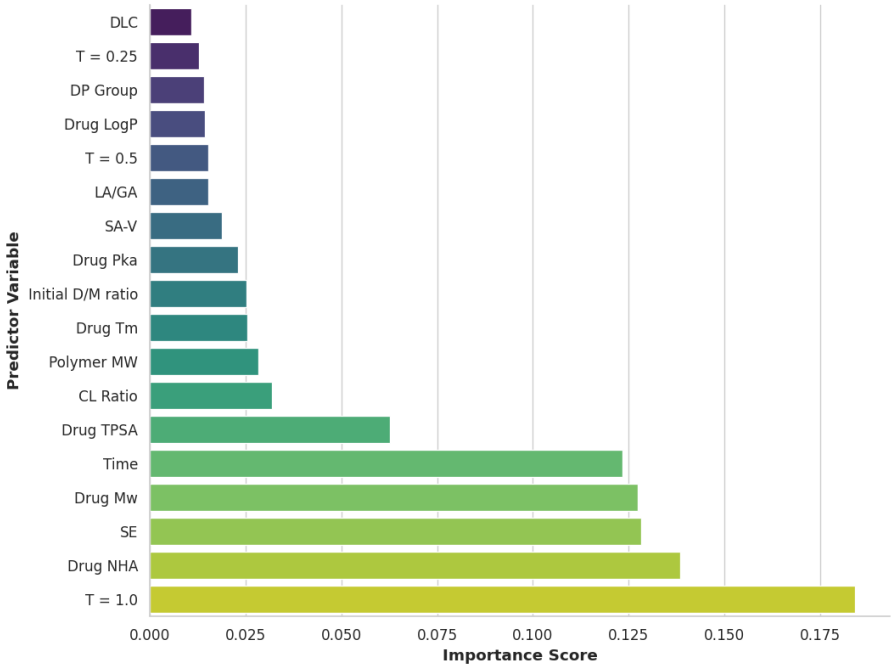

Figure 3. Feature Importance Scores Generated by the XGBoost Regression Model

3.6 Residual Error Analysis

Residual Analysis was done to analyze the stability of the model and also the existence of systematic errors in case of prediction. Minimal prediction bias was found based on relatively symmetric distribution around zero in the case of residuals. Residuals for the optimized XGBoost model are

illustrated in Figure 4 below. Random scattering of residuals around the zero-reference line indicated that there is no systematic relationship between model prediction and range of prediction.

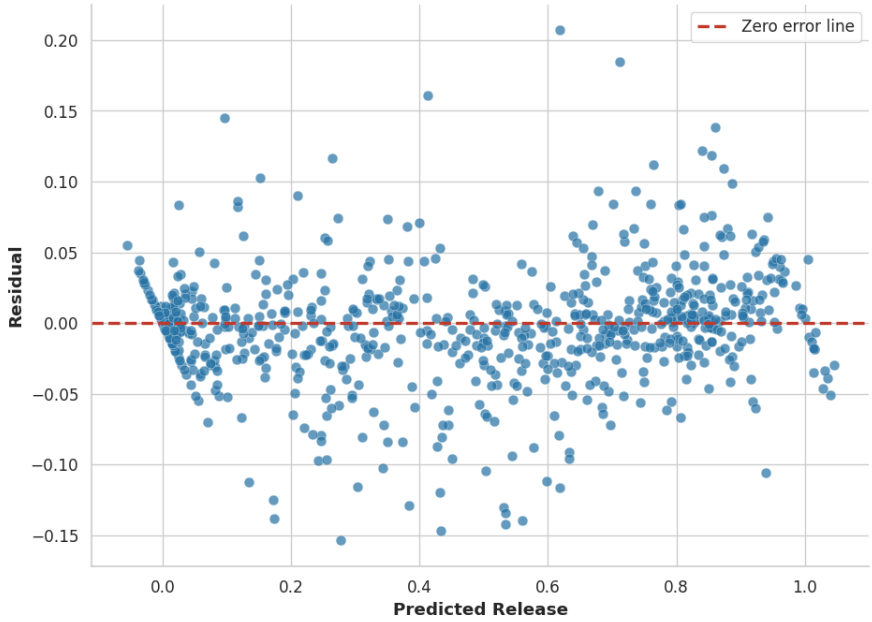

Figure 4. Residual Plot of the Optimized XGBoost Regression Model

The distribution of the residual values proved that the developed model had excellent validity. Most of the residual values were concentrated around zero, while some were present at both ends of the graph. An example of a residual value distribution of the XGBoost model can be seen in Figure 5. The almost normal distribution of the residual values indicated good predictive reliability and statistical validity of the constructed machine learning model.

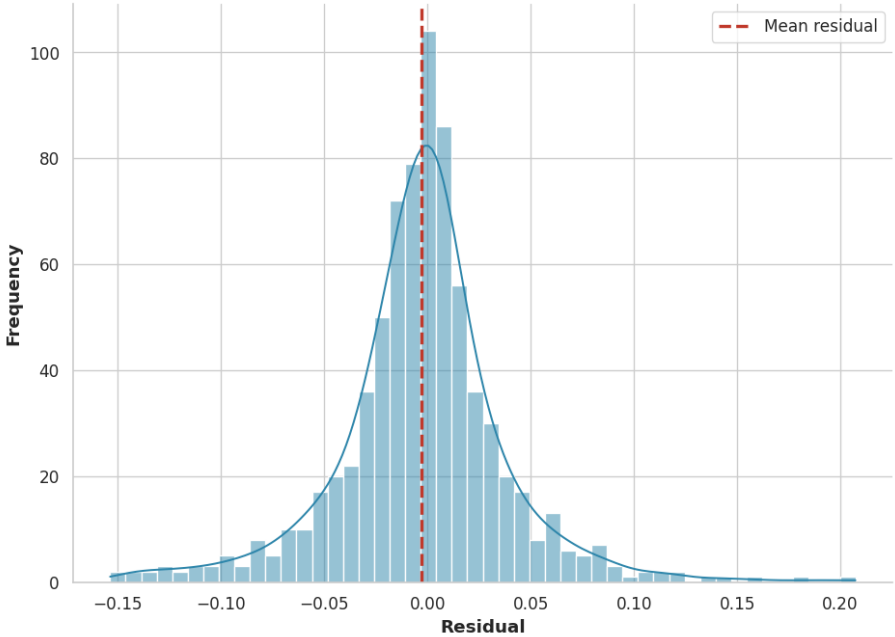

Figure 5. Distribution of Prediction Residuals for the XGBoost Model

4. Discussion

The results reveal that there is a nonlinear interaction between temporal, physicochemical, and formulation-dependent variables which dictate the pattern of drug release from PLAI. The remarkable performance of the proposed ensembles, particularly the XGBoost model, confirms the ability of these advanced regression techniques in predicting the complicated drug release pattern more effectively than linear modeling approaches. With an R2 value of 0.9849, a Mean Absolute Error of

0.0276 and a Root Mean Square Error of 0.0406, the XGBoost model had the highest predictive accuracy. The performance at this level indicates that the model accounted for a high percentage of the variation in release behaviour, with low prediction error. The relatively poor results obtained using Linear Regression are an indication that simple linear relationships are not sufficient to describe release kinetics. The processes involved in the release of the drugs from polymeric systems are complex, and many simultaneous phenomena are involved, such as diffusion, erosion and degradation of the polymer, interaction between the drug and the polymer, and time-related changes in the structure. These processes are not likely to act independently, which is why ensemble-based models were more apt for this prediction task.

Feature importance results also help to understand the most important features that contribute to release prediction. Optimal engineered temporal variable T = 1.0, followed by Drug NHA, SE, Drug Mw, and Time were identified as the most relevant predictors of the response. Thus, it can be assumed that release characteristics strongly depend on the time dependency of the response and the molecular properties of the drug in question. The relevance of such properties as Drug NHA, Drug Mw, and Drug TPSA implies that such drug properties as hydrogen bonding potential, molecular weight, and polarity influence the diffusion of the drug through the polymeric matrices. The relevance of the SE also demonstrates that there is some contribution to the response made by the formulation-related factors associated with structure or surface characteristics of the formulation. The obtained residuals of the optimization process indicate the reliability of the optimized model. Specifically, they were close to zero and showed no clear systematic pattern, which indicates little prediction bias of the model. In addition, the residuals are quite compact around zero value, implying a stable distribution of the predictions. The outliers might be associated with the complexity of predicting the extreme behavior of the boundary response due to formulation effects.

The current results are consistent with recent modelling studies for long acting injectables, which have employed computational tools to describe and predict release profiles. Castiñeiras-Pardines et al. (2025) created a model to characterize the release behavior of the letrozole LAI formulation, highlighting the importance of model-based approaches for understanding release performance. In the same way, Shah and Hong (2022) pointed out the significance of pharmacokinetic and physicochemical properties for depot based long acting injectables to be modeled. The findings and significance of the presence of drug and formulation descriptors in the present work are in line with those reported in polymeric delivery systems. Empirical and predictive models could be used to aid the design of polymer implants with a reservoir by correlating formulation parameters with the release behavior, as reported by Li et al (2022). The results also support the inclusion of the molecular descriptors Drug Mw and Drug NHA since the physicochemical properties of the drug are known to affect the degradation and release kinetics of in-situ forming implants, as demonstrated by Joiner et al. (2022).

The nonlinear behavior modeled in XGBoost is consistent with mechanistic studies that demonstrate that the multiple interacting processes control long-acting injectable release. Furthermore, Sonntag et al. (2023) suggested an accelerated reactive dissolution model for long-acting injectables, which resulted in a complex release model. Additionally, Wang et al. (2025) showed that polymer properties and API attributes influence the performance of in-situ forming implants, emphasizing the significance of formulation and molecular parameters in the current model. Results are also consistent with general studies on long-acting drug delivery systems based on polymers. Polymer delivery systems for long-acting antiretroviral drugs have been identified by Nayan et al. (2024) and have highlighted the importance of sustaining the release control through material and formulation design. The results of this study are in good agreement with the results of Bao et al. (2021), who demonstrated that formulation parameters play a critical role in in vitro release of long-acting injectable suspensions.

Results are relevant to the formulation and pharmaceutical engineering. As shown, XGBoost is able to predict the release behaviour with high accuracy, indicating that ensemble learning can be used to assist in the early stages of formulation screening to estimate the release behaviour without the need for extensive experimental testing. This can lead to decreased workload in the lab, faster development

time, and prioritization of promising drug-polymer combinations. The feature importance results are also explanatory. The model identifies the variables that are most sensitive to the release prediction, which helps to make more informed formulation decisions. When developing polymeric long-acting injectable systems, temporal descriptors, molecule properties, and formulation variables for structural considerations should be viewed as key factors. This enhances the use of explainable machine learning as a predictive and a decision support tool. It is also applicable to quality by design, in which knowledge of the correlation between formulation and product performance is crucial. A good predictive model can help to rationally optimize the formulation and promote the efficiency of sustained-release product development.

Several caveats should be noted. The model was constrained by the variables and experimental conditions used in the analysis, which were secondary data. No external validation with independent formulation data was done. Moreover, feature importance scores are only a measure of predictive relevance and cannot be attributed to direct causality.

Future studies should validate the model with other experimental data and investigate other approaches to explainability, including SHAP analysis. Additional studies can also be conducted to evaluate deep learning, hybrid mechanistic-deep learning models, and experiment-informed optimization workflows for enhanced generalizability and application.

5. Conclusion

The explainable ensemble learning showed good promise for predicting the drug release behavior in polymeric long-acting injectable systems. The results indicate that nonlinear ensemble methods, such as XGBoost, are well-suited to the problem and that XGBoost performed best among the models evaluated. The relatively poor results of Linear Regression indicated that simple linear assumptions do not provide a good description of the release behavior. Temporal descriptors, molecular characteristics and structural formulation variables emerged as important factors in release prediction by feature importance analysis. In particular, T = 1.0, Drug NHA, SE, Drug Mw and Time dominated the model performance, suggesting that both the release progression and the drug-level properties influence the sustained-release behavior. The reliability of the optimized model was also confirmed by the residual analysis, which showed that the prediction bias was low and the distribution of the errors was stable. Results reveal the potential for using interpretable machine learning as a practical decision support tool for formulation screening and optimization. The proposed framework can help lessen the need for substantial experimental trial-and-error methods and help propel data-driven pharmaceutical engineering and more efficient development of polymeric long-acting injectable systems.

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