



FORMULATION-AWARE MACHINE LEARNING OF TIME-DEPENDENT DRUG RELEASE FROM PLGA MICROPARTICLES

NNANGUMA Kingsley Ahamefula

National Centre for Technology Management, Federal Ministry of Innovation Science and Technology,
Modibbo Adama University Yola Nigeria, ORCID: <https://orcid.org/0009-0005-9967-0454>. Email:
kingsleynnangume@gmail.com

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ABSTRACT

Models that rely only on sampling time may overlook formulation properties used to achieve a drug release that varies over time in PLGA microparticles. In this study, the researchers checked if the cumulative in vitro release could be better predicted by the drug or formulation descriptors. A literature-curated database of 321 release experiments and 4,913 measurements were analyzed. Several models using time as well as ten drug and formulation descriptors (histogram-based gradient boosting and random forest) were compared to a time-only boosted base model. Data from source publications were held out for separate validation split, formulation held out complete release curves. The random forest model had a mean absolute error (MAE) of 0.1216, an R^2 of 0.741, and a 31.7% decrease in MAE compared to the time-only baseline. Among the formulation-related variables, time was the most important parameter while the polymer M.W. and drug encapsulation efficiency were less important. On unseen studies, forest performance declined to an MAE of 0.1909 and R^2 of 0.361. Formulation data was more effective at predicting measured release; however, this was less consistent across independent studies. These models should be standardized in terms of release conditions and subsequently be validated before use in formulation selection.

Keywords: PLGA microparticles, drug release kinetics, machine learning, formulation descriptors, external validation



1. Introduction

To extend the action of a drug and decrease the number of doses required, poly(lactide-co-glycolide) (PLGA) microparticles have been developed. Their value is not so much based on a single end-of-formulation measurement of release as on the reliability of a formulation to release over the calculated period of treatment. Leuprolide loaded microspheres have shown to deliver for months in vivo shows the need to control the initial release and sustained exposure (Kim et al., 2022). Recently, PLGA microspheres with engineered release profiles have been studied for extended release over a long bone regeneration period (Li et al., 2026). MSC-CM-loaded PLGA microspheres have also been demonstrated to release over a period of weeks, offering a wider variety of payloads and applications in which a timed assessment is required (Bruk et al., 2023).

The interactions between the drug, polymer matrix, structure of the particles and surrounding medium, cause release from a microparticle to be reflected. Thermal behavior of polymers may affect the mobility of the chains and affect the performance of the drug delivery (Liu & McEnnis, 2022). The layer of skin created on the emulsion droplet surface could also influence the subsequent hardening of the particles and the resulting internal structure (Sharifi et al., 2022). Fabrication studies of PEG-PLGA microparticles have produced particles with tunable particle size which have shown that processing parameters can affect a measurable formulation attribute (Sagoe et al., 2023). A similar batch – microfluidic method has also increased the uniformity of micro-sized particles and their encapsulation efficiency into multichamber PLGA microparticles (Choi et al., 2023). When looking at release, these attributes must be considered along with sampling time.

Another pathway for release trajectories is through composition. The properties and release profiles of aclacinomycin-loaded PLGA-PEG microspheres were modified by varying the amount of PEG (Costa et al., 2025). The formulations and drug selection have been found to provide different release profiles, thus highlighting the diversity of anticancer drug loaded PLGA microspheres (Rahmani et al., 2023). The effect of structure is also evident in micropatterned PLGA films, in which the geometry affected degradation and release, but films are a different dosage form from the microparticles here (Guerriero et al., 2026). Examples like this would help facilitate the recording of both polymer and drug descriptors, without making the assumption that an association found in one delivery system is also found in another without change.

Predicting a full cumulative release curve is more difficult than predicting the release for a specific day. The contributions from early diffusion, changes in the hydrated matrix and later in the polymer degradation can vary with advancing exposure time. Explicit transport assumptions are represented by mathematical simulations in PLGA particles release over time (Sun et al., 2023). A mechanistic model has been developed for PLGA implants, which also demonstrates the benefit of linking the structure of the implant to the release process; however, the geometry of the implants is different from that of microparticles (Mittapelly et al., 2024). Such methods provide a physical interpretation, but assumptions and measurements are required that may not be readily available for literature-derived formulations.

A complementary approach to study relationships between formulation descriptors and repeated release measurements is machine learning. A two-stage model has been suggested to predict the initial behaviors and total release profiles of PLGA microspheres (Song et al., 2026). Neural differential approach has also introduced shape constraints on predicted PLGA release trajectories to provide a more realistic approximation of the actual release (Tang et al., 2026). For long-acting injectables, explainable learning has used time-dependent and time-independent representations, and demonstrated the need for empirical testing, as the choice of model needs to be tested directly against these representations (Robles & Samad, 2026). Other release-prediction studies looked at the factors of polymer degradation, drug loading and microsphere morphology concurrently (Petrov et al., 2026). Together these studies justify the comparison that allows the analysis of the contribution of formulation information to the prediction of results.

That comparison is now possible with an open data set that is literature mined for a broader set of PLGA microparticles. It includes 321 in vitro release experiments and 4,913 different measurements



at various sampling times, along with drug properties and formulation descriptors (Bao et al., 2024). These repeated rows make curves of individual formulations. Randomly splitting the data into training and testing sets would give the same observations belonging to the same curve to both sets, which would give a false sense of the performance of the prediction for a new formulation. Furthermore, there may be multiple versions of a formulation in the same publication, providing a more stringent test for transfer across experimental settings on performance with unseen source studies.

The current study was thus a comparison of a time-only baseline and models that included drug and formulation attributes. It explored the predictions at various phases of release and what inputs to the recorded model were associated with the best performing model. This analysis refers to in vitro, literature curated measurements and does not imply clinical performance or effects of varying individual ingredients. It serves to test if formulation-aware prediction leads to better held-out release estimates and by how much, and how much held-out release estimates improve if source studies are not used in training. The study addressed three objectives:

1. To characterize PLGA microparticle formulations and the distribution of their time-dependent drug release measurements
2. To compare time-only and formulation-aware models on held-out formulations and previously unseen source studies
3. To assess prediction errors across release intervals and identify the recorded variables influencing model performance

2. Materials and Methods

2.1 Study Design and Data Source

The PLGA microparticle dataset (Bao et al., 2024) was used for this data analysis. Data from the processed workbook were the individual measurements of cumulative in vitro drug release, and times of sampling were connected by Formulation Index. A complementary formulation workbook was provided for it that contained drug names, experimental preparation information and publication DOIs. Each release experiment was considered to be a single formulation-level unit and each row of the processed workbook as a measurement. Text fields were trimmed and DOI's defaulted to lower case, and drug identity and source publication were counted. No new compounds or experiments were performed in the laboratory.

2.2 Variables and Data Preparation

The outcome was a continuous measurement of fractional release and sampling time was presented as days. Candidates included were time, drug molecular weight, topological polar surface area, LogP, PLGA molecular weight, lactide-to-glycolide ratio, initial drug-to-polymer ratio, particle size, loading capacity, encapsulation efficiency, and concentration of the solubility enhancers. The DOIs of publications were only added to Formulation Index for study-level validation. There were no missing cells in the processed measurements. Four duplicate formulation-time combinations and 108 release values above one were not removed or clipped and were identified as data-quality limitations.

2.3 Exploratory Analysis of Release Profiles

Data were summarized for numbers of experiments, drugs, publications, sampling points, formulation sizes, and the range of time and fractional release. Points per experiment were calculated based on repeated measurements and grouped by Formulation Index. Sampling dates were considered early (0-1 day), intermediate (more than 1-14 days) or late (more than 14 days) for descriptive reporting. For each interval, counts of experiments and measurements were determined, along with mean and median sampling time, and median and mean release. These summaries are not considered to be independent observations used for uncertainty estimation.

2.4 Model Development



Three regression models were fitted. The principal baseline was a histogram-based gradient boosting model that utilized only the time value. A second histogram-based gradient boosting was used as well as a random forest with the same data as time and the 10 drug and formulation descriptors. Gradient boosting took 200 iterations, 15 maximum leaf nodes, 20 minimum samples per leaf and L2 regularization at 0.1. The forest is constructed from 250 trees, all with a minimum leaf size of three, and 80% of the forest has feature sampling. No tuning of hyperparameters on test data and fixed random seed 42.

2.5 Validation and Performance Assessment

A 80:20 split of the data was done randomly by group and complete release experiments were assigned to training or test sets so as to not give any single curve points to both sets. The 80/20 split was split by publication DOI and analyzed separately from the other 80/20 splits. Each split had models refitted on the training part. The goodness of the held-out predictions, assessed by mean absolute error (MAE), root mean squared error (RMSE) and the coefficient of determination (R^2). Errors were also summed over the three a priori sampling time intervals for the best formulation-held-out model.

2.6 Model Interpretation

Interpretation was based on the model with the lowest test MAE—formulation-held out. By shuffling one predictor at a time and computing MAE on this shuffled test set, the importance of the predictor was determined. Ten replications of each shuffle were performed using a fixed seed with the same set-up and the mean and standard deviation were taken. Importance values thus reflect loss of predictive precision and not a causal effect or even a direction of association. To identify the difference between the drug and the formulation properties, sampling time was added.

3. Results

3.1 Dataset Composition and Quality

The processed file held 4,913 release measurements, for 321 Formulation Index values, which equated to 89 drugs and 113 source publications in the website's companion workbook. We used the median experiment to contribute 13 time points. The sampling period ranged from day 0 to 237.732 with a median sampling time of 8.044 days. The fractional releases measured ranged from 0 to 1.082 with a median of 0.571. These characteristics and quality checks are listed in Table 1. All of the modeled columns were completed, and there were 108 release values above 1 and 4 formulation-time combinations more than once.

Table 1. Characteristics and quality of PLGA microparticle release data

Dataset characteristic	Value
Release measurements	4,913
Release experiments	321
Distinct drugs	89
Source publications	113
Median time points per experiment	13
Sampling time, median (days)	8.044
Sampling time, maximum (days)	237.732
Fractional release, median	0.571



Fractional release, maximum	1.082
Release measurements above 1	108
Duplicate formulation-time combinations	4
Missing cells in modeled data	0

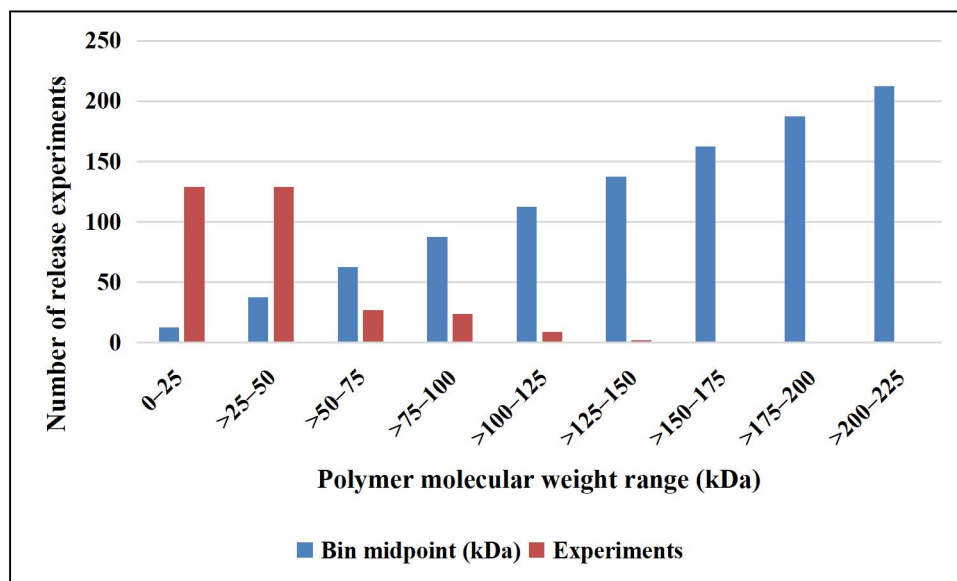


Figure 1. Distribution of polymer molecular weights across formulations

3.2 Observed Release Across Time Intervals

Generally, observed cumulative release was higher for the specified time periods although sampling frequency and time varied by experiment. A total of 771 early measurements have a mean release of 0.125, whereas 2,450 intermediate measurements have a mean release equal to 0.500 and 1,692 late measurements have a mean release equal to 0.746. The median release also increased, from 0.044 to 0.814. Thirty two one experiments were registered during the early interval and 250 experiments during the late interval after day 14 (Table 2). Thus, between-interval variations are due to both time elapsed and the changing representation of formulations and should not be seen as within-formulation variations.

Table 2. Observed drug release across three sampling intervals

Sampling interval (days)	Measurements	Experiments	Median time (days)	Mean fractional release	Median fractional release
0–1	771	321	0.157	0.125	0.044
>1–14	2,450	320	6.000	0.500	0.516
>14	1,692	250	22.936	0.746	0.814

3.3 Predictive Performance on Held-Out Data

Formulation-held-out test set compared with a separate test set held out for evaluation. The MAE and R^2 of the boosting baseline with the time-only was 0.1780 and 0.550 respectively on the unseen formulations. The formulation variables slightly increased the boosting MAE to 0.1306, and the random forest provided the lowest MAE of 0.1216, which was a 31.7% improvement from the



baseline (Table 3). When applying the same analysis to the unseen studies, the performance was not as promising with the MAE for random forest rising to 0.1909 and the R^2 dropping to 0.361. The study-held out boosting was not as effective as its time-only counterpart. The R^2 obtained for forest training was 0.964 (Figure 3).

Table 3. Predictive performance across formulation and study holdouts

Validation set	Model	Test measurements	Test experiments	MAE	RMSE	R^2
Unseen formulations	Time-only boosting	978	65	0.1780	0.2230	0.550
Unseen formulations	Formulation-aware boosting	978	65	0.1306	0.1753	0.721
Unseen formulations	Formulation-aware forest	978	65	0.1216	0.1692	0.741
Unseen studies	Time-only boosting	964	54	0.2095	0.2654	0.326
Unseen studies	Formulation-aware boosting	964	54	0.2178	0.3059	0.105
Unseen studies	Formulation-aware forest	964	54	0.1909	0.2584	0.361

Note. The two validation sets came from separate splits and separately fitted models. MAE and RMSE use fractional-release units.

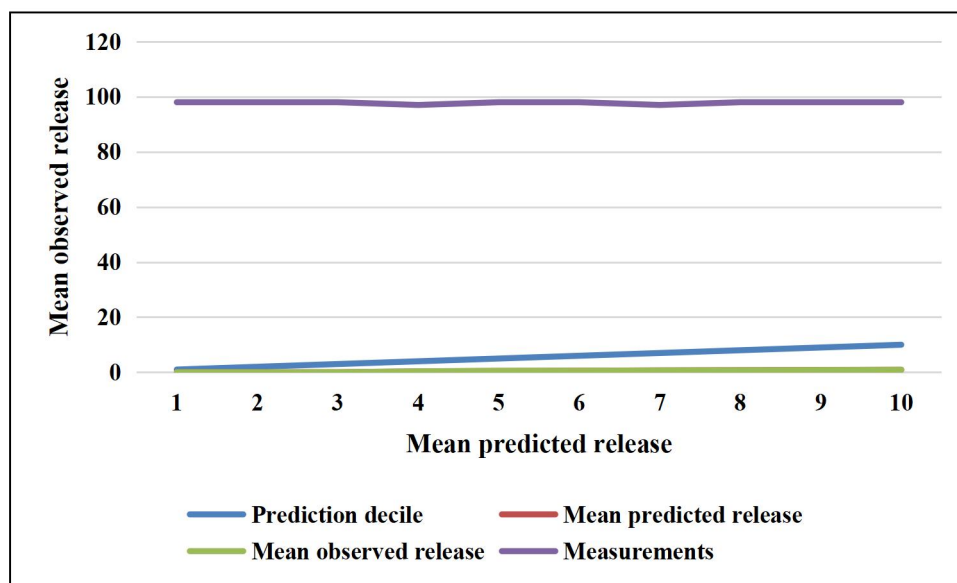


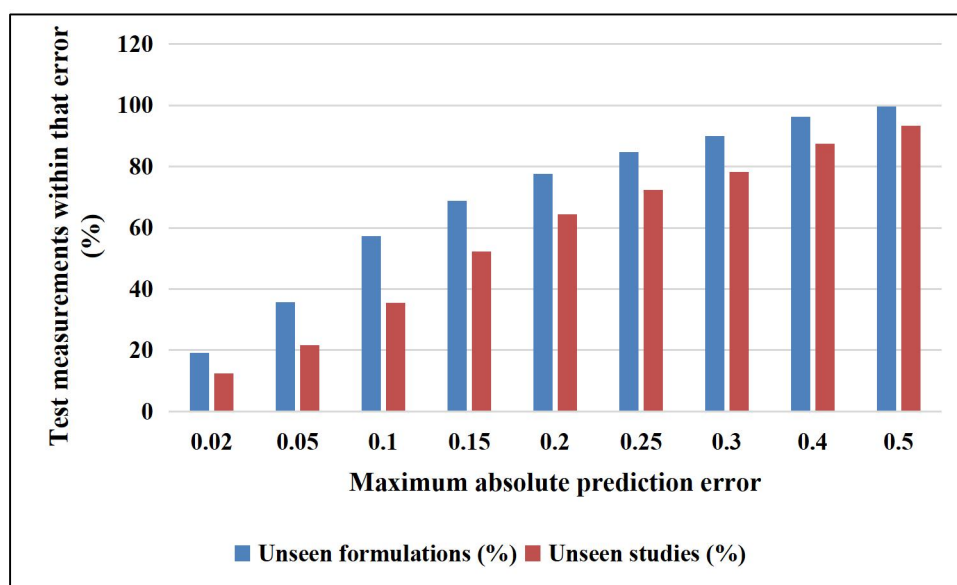
Figure 2. Binned predicted versus observed release in testing

3.4 Accuracy by Release Interval

Predictions of the random forest from the formulation held out samples by sampling interval. The lowest error occurred on day 1 with MAE value of 0.0510 for 167 measurements, and the highest occurred between day 1 and day 14 with MAE 0.1498 for 443 measurements. The MAE on day 14 was 0.1196 for 368 measurements from 53 experiments after day 14. The corresponding R^2 values were 0.638, 0.536, and 0.335 (Table 4). These comparisons are confounded by different release distributions and/or experiment coverage of intervals, which is why the estimates represent predictive behavior in each interval and not a controlled time effect.

**Table 4. Random forest prediction accuracy across release intervals**

Test interval (days)	Measurements	Experiments	MAE	RMSE	R ²
0–1	167	65	0.0510	0.0842	0.638
>1–14	443	65	0.1498	0.1959	0.536
>14	368	53	0.1196	0.1631	0.335

**Figure 3. Prediction error tolerance across two validation designs**

3.5 Importance of Formulation Descriptors

The formulation held-out forest was then used to test a permutation analysis of the formulation, which found that the main contributor was sampling time with a test MAE increase of 0.2229. Non-time variables that showed the greatest increase were polymer molecular weight (0.0264), drug encapsulation efficiency (0.0200), and drug molecular weight (0.0135) (Table 5). Any reported values are the average of 10 permutations. These indicate how dependent this trained model is on each recorded input. Predictive information is possible to be shared between correlated formulation variables, and no importance value would be used to declare that the release change for a formulation property was caused by changing another formulation property.

Table 5. Permutation importance of time and formulation predictors

Predictor	Increase in test MAE	SD across 10 permutations
Time	0.2229	0.0084
Polymer molecular weight	0.0264	0.0018



Drug encapsulation efficiency	0.0200	0.0015
Drug molecular weight	0.0135	0.0008
Drug loading capacity	0.0088	0.0009
Drug topological polar surface area	0.0073	0.0009
Initial drug-to-polymer ratio	0.0067	0.0005
Particle size	0.0059	0.0005
Drug LogP	0.0042	0.0008
Lactide-to-glycolide ratio	0.0033	0.0004
Solubility enhancer concentration	0.0031	0.0005

4. Discussion

Drug and formulation descriptors were found to be able to predict cumulative release better than sampling time alone if entire formulations were held out. Random forest yielded test MAE of 0.1216 fractional-release units, a 31.7% reduction, along with an R^2 of 0.741. This is consistent with the notion that the released fraction does not necessarily equal the elapsed time for each formulation. However, the increase needs to be viewed in the context of the in vitro protocols of the dataset. A literature review on PLGA long-acting injectable testing revealed that there are significant differences in the release apparatus and conditions, and there is no single method appropriate for any particular product (Kregar et al., 2026).

Table 3 verified the seemingly robust formulation-held-out result with difference between the designs. Forest MAE increased to 0.1909 and R^2 decreased to 0.361 when baseline was the source publications instead of formulations; baseline was time-only when MAE was 0.2095. The formulating inputs therefore still gave a relatively less improvement in MAE of 8.9%, and the boosting model was inferior to the time only model. One likely unmeasured contributor is the difference in the temperature of the release media. Temperature was found to affect the matrix formation, degradation, and burst release from PLGA in-situ forming implants (Shafiee et al., 2024). That study recognizes that there could be a source of heterogeneity and doesn't necessarily point to error in that dataset.

Table 4 and Figure 5 identified differential difficulty in predicting, in terms of time. The starting levels on the first day of forest MAE were many zeros, 0.0510, and 0.1498 for days 1-14, and 0.1196 for days 15-20. Lower error of it cannot prove better prediction of an actual initial burst. In another PLGA microparticle study, the in vitro release duration of the two drugs, carboplatin and etoposide, were significantly different, even though they are transported by a mixed therapeutic formulation (Shinde et al., 2024). The difference was similar to what is needed for representing drug properties, but the present analysis was not conducted on simultaneous release of two compounds and did not include a representation of the ocular application.

Time was found to be the most important entry among all formulation-related inputs while polymer MW, EE, and drug MW were ranked 2nd, 3rd, and 4th, respectively. These rankings show which recorded values the fitted forest used, but do not assess the impact of any recorded value being varied, while keeping the others constant. The study by Lee et al., 2023, was a study of pH-responsive PLGA/Eudragit microparticles with a deliberate modification of the release through a hybrid polymer and environmental response. Polymer blends were also employed for the delivery of breast cancer,



specifically targeted microspheres of PLGA-PCL (Nwazojie et al., 2023). It is important to note that the present processed predictors did not include any hybrid composition or pH response, so they do not cover extrapolations to hybrid designs.

As can be seen in Figure 2, significant differences exist between the formulations of the same drug, especially in the early release of the drug. These are still descriptive examples and not evidence that it was particle size that caused those differences. This is more critical in more complex systems. For a cartilage-regeneration study, dual microparticles were programmed into a tissue-specific hydrogel to deliver the program across a biological process (Ran et al., 2024). Comparing models with each other, the present models predict the release fractions from individual, literature-curated PLGA microparticle experiments. Their prediction of coordinated release from multiple carriers or the effect of an enclosing hydrogel can be done without providing relevant training measurements.

The release of a drug in vitro should not be interpreted as its therapeutic effect. The study of vortioxetine loaded PLGA microspheres for local brain delivery reported sustained release for around 1 month plus separate biological testing, which necessitated experiments not just on a release curve (Wang, 2025). The dataset in the present study was not examined for cellular uptake for liver cancer cells, which was studied for sorafenib-loaded PLGA nanocarriers, but these nanocarriers are much smaller than that of the present study (Caputo et al., 2023). In addition, light-responsive release was studied with gold associated PLGA nanoparticles, where the external trigger is a light source (Erdoğan et al., 2024). These systems demonstrate the need for performance to be translated into the nanoparticle, triggered delivery and clinical applications.

There are a number of aspects of the analysis that warrant care. The source consisted of a compilation of published release curves that had different sampling schedules, and 108 measurements were above a fractional release; four formulation-time combinations were duplicated. Keeping those records prevented undocumented corrections, but could affect fitted errors. There was only one group split and no uncertainty across alternative study selections was estimated. Formulation characteristics such as encapsulation efficiency and loading capacity are measured characteristics, and cannot be predicted as forecasts before manufacture of the formulation. Experimental media and temperature and morphology should be recorded more fully in the future, as should study provenance; repeated source-held-out splits should be evaluated and new laboratory formulations tested prospectively. This would establish the range of possible formulations for which models can aid in screening decisions.

5. Conclusion

The time-dependent in vitro release from PLGA microparticles is better predicted, by adjusting the drug and formulation characteristics. For held-out formulations, the formulation aware random forest showed an MAE of 0.1216 and R^2 of 0.741 across 321 experiments and 4,913 release measurements. This MAE was 31.7% lower than the baseline of the time-only model. Sampling time was the most predictive parameter, and polymer molecular weight, encapsulation efficiency, and drug molecular weight were predictive parameters which provided further information. The highest error was observed on days 1 thru 14, indicating that the model was not performing consistently throughout the release period. When whole source studies were not included in the model (whole source studies excluded), the forest MAE rose to 0.1909 and the R^2 fell to 0.361. This difference suggests that the performance in unfamiliar experimental conditions needs to be investigated further. The results presented are relationships that were observed in literature-derived release measurements and do not explain the direct result of a change of a formulation characteristic, nor do they predict in vivo results. The current model is most appropriate for screening characterised formulations, as loading capacity and encapsulation efficiency are measured after preparation. Further investigations should include a more standardized record of release parameters, a replication of the validation in independent investigations, and a test of predictions with microparticles prepared in advance. These steps would help in better understanding of its value in the selection of sustained delivery candidates.



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