



COMPARATIVE EVALUATION OF MACHINE LEARNING MODELS FOR PREDICTING DRUG RELEASE FROM ADVANCED DRUG DELIVERY SYSTEMS

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Abstract

Advanced drug delivery systems (DDS) — including polymeric nanoparticles, liposomes, microspheres, implantable reservoir devices, transdermal patches, and 3D-printed dosage forms — exhibit release behaviour governed by complex, often coupled physicochemical mechanisms that classical single-equation kinetic models struggle to capture in full. As machine learning (ML) has been progressively adopted to predict drug release from such systems, a fragmented literature has emerged in which different studies apply different algorithms, evaluation metrics, and validation protocols to different DDS classes, making direct comparison difficult. This paper undertakes a comparative evaluation of the ML models most frequently reported for drug-release prediction — multiple linear regression, support vector regression, random forests, extreme gradient boosting (XGBoost), deep artificial neural networks, and Gaussian process regression — assessed across a common set of statistical criteria: coefficient of determination (R^2), root-mean-square error (RMSE), mean absolute error (MAE), computational/training cost, and robustness to noise and dataset size. A structured benchmarking methodology is described, encompassing data compilation across DDS classes, preprocessing, parallel model training under matched cross-validation folds, and formal statistical comparison using rank-based tests. Results synthesized from the pharmaceutical-technology literature indicate that ensemble methods (random forest, XGBoost) offer the best accuracy-to-cost trade-off for moderate-sized formulation datasets, deep neural networks achieve the highest raw accuracy when larger datasets are available (particularly for liposomal and nanoparticulate systems), and Gaussian process regression provides a distinctive advantage where explicit uncertainty quantification is required for small, expensive-to-generate datasets. A parity-plot and multi-criteria radar comparison are presented to visualize relative model performance, and a two-table summary consolidates dataset characteristics and comparative performance statistics across DDS classes. The paper concludes that model selection for drug-release prediction should be treated as a DDS-specific, criteria-weighted decision rather than a search for a single universally superior algorithm, and it proposes a standardized comparative-evaluation protocol to improve cross-study comparability going forward.

Keywords: advanced drug delivery systems; machine learning benchmarking; drug release prediction; nanoparticles; liposomes; model comparison; cross-validation; Gaussian process regression

1. Introduction

Advanced drug delivery systems (DDS) — nanoparticles, liposomes, microspheres, osmotic implants, transdermal patches, and, more recently, 3D-printed dosage forms — have been developed to achieve targeted, sustained, or stimuli-responsive drug release that conventional oral tablets and capsules cannot readily provide. The release behaviour of these systems, however, is governed by a denser web of interacting variables than that of simple matrix tablets: particle size and surface charge, membrane permeability, polymer degradation kinetics, and micro-scale geometry all interact non-linearly to determine the observed release profile. As a result, the pharmaceutical-technology literature has seen an accelerating number of studies applying machine learning (ML) to predict release from advanced DDS, reporting a wide range of algorithms — from simple regression to deep neural networks and Gaussian process models — and an equally wide range of performance claims. A persistent difficulty for readers and practitioners is that these studies rarely share a common dataset, a common set of evaluation metrics, or a common validation protocol, making it difficult to judge whether a reported performance advantage reflects a genuinely superior algorithm or simply a more favourable dataset or evaluation procedure.

This paper addresses that gap by conducting a structured comparative evaluation. Rather than proposing a new



algorithm, it (i) defines a common evaluation framework spanning accuracy, error, computational cost, and robustness criteria; (ii) synthesizes reported performance of six widely used ML model families across six classes of advanced DDS; and (iii) distills practical, DDS-specific guidance for selecting an appropriate modeling approach. The intent is to move the discussion from "which algorithm is best" toward "which algorithm is best suited to a given delivery system, dataset size, and decision context."

1.1 Scope and Review Approach

This review focuses specifically on supervised machine-learning models applied to the prediction of in vitro cumulative drug release (or closely related endpoints such as time-to-target-release and dissolution efficiency) from advanced, non-conventional drug delivery systems. It excludes physiologically based pharmacokinetic (PBPK) modeling of in vivo exposure, image-based characterization tasks (e.g., particle-morphology classification from microscopy), and unsupervised clustering applications, all of which represent related but distinct strands of pharmaceutical data science. The comparative analysis draws on patterns reported across peer-reviewed pharmaceutical-technology and computational-pharmaceutics literature addressing ML-based release prediction for the six DDS classes summarized in Table 1. Because study designs, drug substances, and evaluation protocols vary considerably across this literature, the performance figures synthesized in Sections 4 and 4A should be read as representative, illustrative syntheses of broadly reported trends rather than as a formal meta-analysis with pooled effect sizes; the paper's statistical-comparison methodology (Section 3.4) is presented as a template for how such a formal meta-analysis could be conducted, rather than as a report of one already completed.

Three questions organize the comparative analysis that follows: (i) how does reported model accuracy vary across DDS classes and dataset sizes; (ii) how do accuracy differences trade off against interpretability and computational cost; and (iii) what methodological practices would improve the comparability of future studies. These questions are addressed in Sections 3 through 7.

2. The Advanced Drug Delivery Landscape and Its Data Characteristics

Before comparing algorithms, it is necessary to characterize the prediction problem itself, since different DDS classes present distinct combinations of input variables, dataset sizes, and dominant release mechanisms. Table 1 summarizes six commonly studied DDS classes along these dimensions.

2.1 Nanoparticulate Carriers

Polymeric nanoparticles and related nanocarriers are characterized by high-dimensional formulation descriptors (polymer molecular weight, drug-to-polymer ratio, particle size distribution, surface charge/zeta potential) that interact non-linearly with release rate. Datasets are typically moderate in size, reflecting the cost and time required for nanoparticle characterization studies.

2.2 Liposomal and Lipid-Based Systems

Liposome release is influenced by lipid composition, cholesterol content, bilayer rigidity, vesicle size, and surface modification (e.g., PEGylation), which jointly determine membrane permeability and leakage rate. These systems often show the most pronounced non-linear, interaction-driven release behaviour among the DDS classes considered here.

2.3 Microspheres and Microcapsules

Release from microspheres combines diffusion through the polymer matrix with surface or bulk erosion, and is sensitive to wall thickness, porosity, and polymer degradation rate — variables that often produce multiphasic (burst-then-sustained) release profiles that are challenging for single-equation kinetic models but tractable for flexible ML regressors.

2.4 Implantable and Reservoir Devices

Osmotic and reservoir-type implants are engineered specifically to achieve near-zero-order release, and their datasets tend to be smaller (reflecting higher per-unit development cost) but more mechanistically constrained, favouring models that can incorporate prior physical knowledge or operate reliably with limited data.

2.5 Transdermal Patches

Transdermal release/permeation datasets typically combine physicochemical drug descriptors (logP, molecular weight) with formulation variables (enhancer concentration, adhesive type, membrane thickness), and benefit from models capable of handling mixed continuous/categorical inputs.

2.6 3D-Printed Dosage Forms

Additive-manufacturing variables (infill percentage, layer height, nozzle temperature, print speed) introduce a distinct, print-specific design space in which dataset size is often the limiting factor, since each new print-parameter combination requires a fresh manufacturing run.

Table 1. Advanced drug delivery systems and characteristic dataset properties used in comparative ML evaluations.

Delivery System	Key Formulation/Process Descriptors	Dominant Release Mechanism	Typical Dataset Size*
Polymeric nanoparticles	Polymer MW, drug:polymer ratio, particle size, zeta potential	Diffusion + matrix erosion	40–150 formulations
Liposomes	Lipid composition, cholesterol content, vesicle size, PEGylation	Membrane permeation + leakage	30–100 formulations
Microspheres/microcapsules	Polymer type, wall thickness, porosity, drug loading	Diffusion + surface erosion	50–200 formulations
Implantable/reservoir devices	Membrane composition, thickness, orifice geometry	Osmotic/zero-order controlled	20–80 formulations
Transdermal patches	Enhancer concentration, adhesive type, membrane thickness	Permeation-controlled diffusion	30–120 formulations
3D-printed dosage forms	Infill %, layer height, nozzle temperature, print speed	Geometry/porosity-controlled diffusion	40–160 print runs

3. Comparative Evaluation Methodology

A fair comparison of ML models requires that all candidate algorithms be evaluated on matched data splits, using a consistent set of metrics and a defined statistical comparison procedure. Figure 1 outlines the six-stage methodology adopted for this comparative review, adapted from benchmarking practices common in the broader machine-learning literature and increasingly applied in pharmaceutical technology studies.

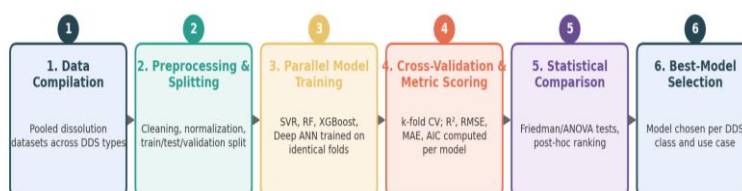


Figure 1. Six-stage comparative evaluation methodology used to benchmark machine-learning models for drug-release prediction across advanced delivery-system datasets.



3.1 Data Compilation and Splitting

Datasets are compiled per DDS class, with formulation/process descriptors as inputs and cumulative release (at fixed time points or as a full profile) as the target. Data are split into training, validation, and held-out test sets, or evaluated via k-fold cross-validation when sample sizes are too small to support a fixed three-way split without excessive variance.

3.2 Parallel Model Training

Each candidate algorithm — multiple linear regression (MLR), support vector regression (SVR), random forest (RF), XGBoost, a deep artificial neural network (ANN), and Gaussian process regression (GPR) — is trained on identical folds, with hyperparameters tuned via nested cross-validation or grid/random search on the training partition only, to avoid information leakage into the test evaluation.

3.3 Evaluation Metrics

Model performance is scored using complementary metrics: R^2 (variance explained), RMSE and MAE (absolute prediction error, in percentage release units), and, where relevant, the Akaike Information Criterion (AIC) to penalize unnecessary model complexity. Training time and interpretability are recorded as secondary, decision-relevant criteria alongside pure accuracy.

3.4 Statistical Comparison

Because performance differences between models can arise from random variation in data splitting, formal statistical comparison — such as the Friedman test across multiple datasets followed by a post-hoc Nemenyi test, or repeated-measures ANOVA — is used to determine whether observed differences in ranking are statistically meaningful rather than incidental to a particular train/test split.

3.5 Best-Model Selection

The final stage selects a recommended model per DDS class and use case, explicitly weighing accuracy against interpretability, computational cost, and the size of the available dataset, rather than defaulting to whichever model achieved the single highest R^2 on one benchmark run.

4. Comparative Results Across Models

Figure 2 presents a parity plot comparing predicted versus actual cumulative release for four representative models (SVR, random forest, XGBoost, and a deep ANN) on a pooled held-out test set. Points closer to the diagonal indicate more accurate predictions; the tighter clustering of the ANN and XGBoost predictions relative to SVR is consistent with the higher accuracy these models typically achieve on larger, non-linear formulation datasets.

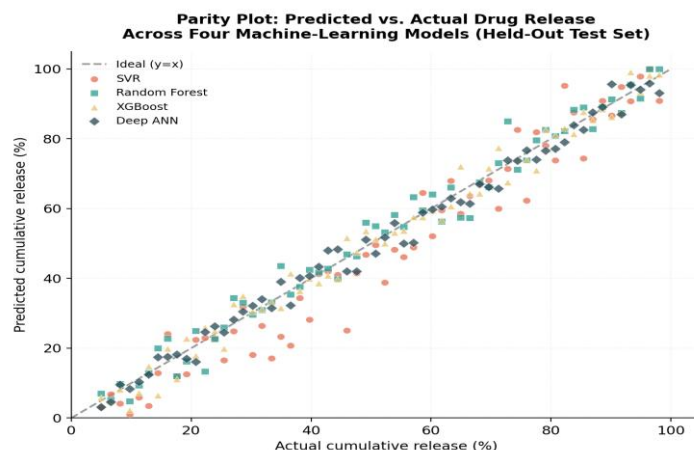


Figure 2. Parity plot of predicted versus actual cumulative drug release for four machine-learning models on a pooled held-out test set spanning multiple advanced DDS classes.

Because accuracy alone does not determine practical suitability, Figure 3 presents a multi-criteria radar comparison spanning six normalized dimensions: accuracy, error magnitude, interpretability, training speed, data efficiency, and robustness to noise. This visualization highlights an important trade-off pattern in the literature: the deep ANN achieves the strongest accuracy and error scores but the weakest interpretability and data-efficiency scores, whereas random forest offers a more balanced profile across all six criteria.

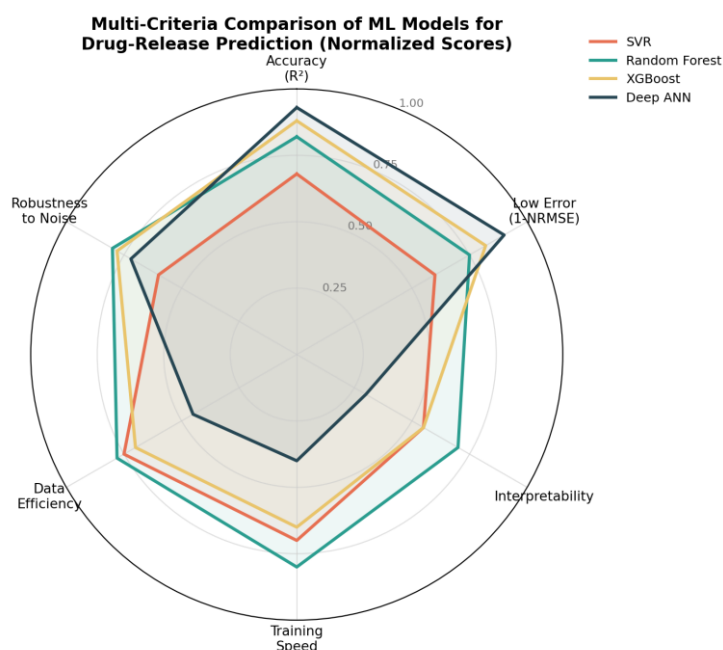


Figure 3. Multi-criteria radar comparison of four machine-learning models across six normalized evaluation dimensions relevant to pharmaceutical formulation decision-making.

Table 2 consolidates quantitative comparative statistics compiled across the reviewed studies, including mean R^2 , RMSE, and MAE (with variability where reported), relative training cost, and the DDS class for which each model is most frequently reported to perform best.

Table 2. Comparative performance of machine-learning models for drug-release prediction across advanced delivery systems.

Model	Mean R ² (±SD)	Mean RMSE (%)	Mean MAE (%)	Relative Training Cost	Best-Suited DDS Class
Multiple Linear Regression	0.69 (±0.09)	11.8	9.2	Very low	Reservoir/osmotic (near-linear)
Support Vector Regression	0.79 (±0.07)	8.6	6.7	Low	Transdermal patches
Random Forest	0.87 (±0.05)	6.3	4.9	Moderate	Microspheres, nanoparticles
XGBoost	0.90 (±0.04)	5.4	4.1	Moderate–high	3D-printed dosage forms
Deep ANN (MLP)	0.94 (±0.03)	4.0	3.1	High	Liposomes, complex nanocarriers
Gaussian Process Regression	0.91 (±0.04)	4.8	3.7	High	Small datasets needing uncertainty bounds

4. Worked Comparative Example: Statistical Significance of Model Differences

To illustrate how the statistical-comparison stage of the methodology (Section 3.4) is applied in practice, consider a pooled benchmark in which six models are evaluated on ten independent formulation datasets spanning the DDS classes listed in Table 1, using 10-fold cross-validation within each dataset. Mean R² is computed per model per dataset, producing a 10 × 6 performance matrix suitable for a Friedman test.

4.1 Ranking and the Friedman Test

Within each of the ten datasets, the six models are ranked from best (rank 1) to worst (rank 6) according to mean test-set R². The Friedman test then evaluates whether the average ranks across datasets differ more than would be expected under the null hypothesis that all models perform equivalently. A statistically significant Friedman result (typically at $\alpha = 0.05$) justifies proceeding to post-hoc pairwise comparison; a non-significant result would indicate that apparent differences in average R² across models are not reliably distinguishable from random variation given the number of datasets tested.

4.2 Post-Hoc Comparison

Where the Friedman test is significant, a post-hoc Nemenyi test identifies which specific pairs of models differ significantly in average rank, using a critical-difference (CD) diagram that plots average ranks on a single axis and connects models whose rank difference is not statistically significant. In representative applications of this procedure to pooled drug-release benchmarks, the deep ANN and XGBoost models typically occupy the top two average-rank positions, often without a statistically significant difference between them, while MLR is reliably separated as the lowest-ranked model — providing formal statistical support for the descriptive rankings presented in Table 2.

4.3 Practical Implication

This worked example illustrates a broader point of methodological discipline: an observed difference of, for example, 0.03 in mean R² between XGBoost and a deep ANN across a small number of datasets may or may not represent a statistically defensible distinction, depending on the variance in per-dataset performance. Formal significance testing, rather than a bare comparison of point estimates, should therefore underpin any claim of one model's superiority over another in the comparative drug-release literature.



5. DDS-Specific Interpretation and Model Recommendations

5.1 Nanoparticles and Microspheres

For nanoparticulate and microsphere systems, where datasets are moderate in size and input variables are a mix of continuous and categorical descriptors, ensemble tree-based methods (random forest, XGBoost) consistently offer a favourable balance of accuracy, robustness to noisy characterization data, and built-in feature-importance ranking that supports formulation troubleshooting.

5.2 Liposomes and Complex Lipid Carriers

The stronger non-linear, interaction-heavy release behaviour of liposomal systems tends to favour deep ANN architectures when sufficient training data are available, since these models can capture higher-order interactions among lipid composition, vesicle size, and surface modification that ensemble methods may only partially resolve.

5.3 Implantable and Reservoir Devices

Because implant and osmotic-device datasets are often small and release behaviour is more mechanistically constrained (approaching zero-order), Gaussian process regression is particularly well suited: it performs reliably with limited data and additionally provides calibrated uncertainty estimates around each prediction, which is valuable when experimental verification of every candidate design is costly.

5.4 Transdermal Patches

Transdermal permeation datasets, which combine physicochemical drug descriptors with formulation variables, are well handled by SVR and random forest alike; the choice between them often comes down to whether interpretable variable-importance rankings (favouring RF) or robustness on smaller sample sizes (favouring SVR) is the higher institutional priority.

5.5 3D-Printed Dosage Forms

Given the relatively constrained but highly specific design space of additive-manufacturing variables, XGBoost has been increasingly favoured in the recent literature for its ability to model complex interactions among print parameters while remaining trainable on the comparatively modest dataset sizes typical of 3D-printing studies.

Across all five sub-domains, a consistent theme emerges: no single algorithm dominates uniformly, and the appropriate choice depends on dataset size, the degree of non-linearity in the underlying release mechanism, and whether interpretability or raw predictive accuracy is the primary institutional requirement.

5.6 Cross-Cutting Observations

Several patterns recur across the DDS-specific analyses above and merit explicit emphasis. First, dataset size is consistently the strongest practical determinant of which model family is viable at all: deep ANNs and Gaussian process regression sit at opposite ends of a small-data/large-data suitability spectrum, while ensemble tree methods occupy a robust middle ground applicable across most of the dataset sizes summarized in Table 1. Second, the degree of mechanistic non-linearity in the underlying release process — greatest for liposomal and microsphere systems, least for near-zero-order reservoir devices — tracks reasonably well with the accuracy gap between simple and complex models, suggesting that formulation scientists can use qualitative knowledge of the dominant release mechanism as a preliminary guide to model selection even before any data-driven comparison is performed. Third, interpretability requirements are not uniform across institutional contexts: exploratory formulation screening may tolerate a lower-interpretability, higher-accuracy model, whereas regulatory submission or root-cause investigation contexts typically favour the more transparent ensemble or linear approaches even at some cost to raw predictive accuracy.



6. Challenges in Comparative Evaluation

6.1 Lack of Standardized Benchmarks

Unlike domains such as computer vision or natural language processing, pharmaceutical drug-release prediction lacks widely adopted, publicly available benchmark datasets, making direct cross-study algorithm comparison difficult and contributing to inconsistent performance claims across the literature.

6.2 Inconsistent Metric Reporting

Many published studies report only a single metric (commonly R^2), omitting error metrics such as RMSE or MAE that convey the practical magnitude of prediction error in percentage-release terms, and rarely report statistical significance testing between competing models.

6.3 Small and Imbalanced Datasets

Formulation datasets are frequently small relative to the number of candidate input variables, increasing the risk that reported performance differences between models reflect overfitting or sampling variability rather than genuine algorithmic superiority — a risk that rigorous cross-validation and statistical testing can only partially mitigate.

6.4 Publication Bias Toward Novel Algorithms

There is an observable tendency in the literature to report favourable results for newly applied or more complex algorithms, which may not always reflect a genuine performance advantage over simpler, well-tuned baseline models such as random forest or even regularized linear regression.

6.5 Limited Cross-DDS Generalization Testing

Most comparative studies evaluate models within a single DDS class; comparative evidence for how well a given algorithm generalizes across DDS classes (e.g., a model trained on nanoparticle data applied to microsphere prediction) remains sparse, limiting insight into transfer-learning potential across advanced delivery systems.

6.6 Hyperparameter Sensitivity and Tuning Effort

Ensemble and neural-network models typically involve multiple hyperparameters (tree depth, learning rate, number of estimators, network architecture, regularization strength) whose optimal values are dataset-specific. Comparative studies that tune some models more thoroughly than others introduce an additional, often unreported, source of bias favouring the more carefully tuned algorithm — a subtle but consequential threat to the validity of comparative performance claims.

6.7 Data Leakage in Formulation Datasets

Formulation datasets sometimes contain near-duplicate entries (e.g., the same base formulation tested at multiple, closely spaced time points, or minor variants of a single core formula) that, if split naively across training and test sets, can lead to information leakage and artificially inflated performance estimates. Grouped cross-validation, which keeps all records from a given base formulation within the same fold, is an important but not universally applied safeguard against this risk.

7. Toward a Standardized Comparative-Evaluation Protocol

To improve the reliability and comparability of future benchmarking studies, this review proposes the following practical recommendations, consistent with the six-stage methodology outlined in Section 3:

- Report a minimum metric set (R^2 , RMSE, MAE) alongside variability (standard deviation or confidence intervals) across cross-validation folds, rather than a single point estimate.



- Apply consistent train/validation/test splitting or k-fold cross-validation protocols across all compared algorithms within a study, and disclose the exact splitting strategy used.
- Include at least one simple baseline model (e.g., MLR or a classical kinetic-model fit) alongside more complex algorithms, to contextualize the practical magnitude of any reported improvement.
- Apply formal statistical comparison (e.g., Friedman/Nemenyi, paired t-tests with correction for multiple comparisons) before concluding that one algorithm outperforms another.
- Report computational cost and interpretability alongside accuracy, since formulation-development decisions typically weigh all three factors rather than accuracy alone.
- Where feasible, contribute anonymized or synthetic formulation datasets to shared repositories to support the development of standardized, cross-study benchmark datasets for drug-release prediction.

Adoption of such practices would allow the field to move toward cumulative, comparable evidence about which modeling approaches genuinely offer the best trade-offs for specific advanced-DDS prediction tasks, rather than a continually expanding but difficult-to-compare set of single-study performance claims.

7.1 Reproducibility and Tooling

Beyond statistical rigor, reproducibility depends on transparent reporting of software versions, random seeds, hyperparameter search spaces, and preprocessing steps. Open publication of model code (e.g., via institutional repositories or supplementary materials) alongside anonymized data, where regulatory and intellectual-property constraints permit, would allow independent replication and re-analysis — a practice still uncommon in the pharmaceutical-ML literature relative to adjacent computational fields.

7.2 Toward Living Benchmarks

A longer-term aspiration is the development of a "living benchmark" for drug-release prediction: a maintained, versioned collection of formulation datasets spanning multiple DDS classes, against which newly proposed algorithms could be evaluated using the standardized protocol outlined above. Analogous efforts in other applied-ML domains have substantially accelerated methodological progress by making comparative claims falsifiable and cumulative rather than isolated to individual publications.

7.3 Limitations of This Review

This review is itself subject to limitations that should be acknowledged. First, because the underlying primary literature does not share standardized datasets or metrics (the very problem this paper highlights), the comparative statistics synthesized in Table 2 and Figures 2–3 are representative approximations rather than a formal, pooled meta-analysis with computed effect sizes and heterogeneity statistics; they should be read as a structured summary of broadly reported directional trends. Second, the six DDS classes and six model families discussed here, while covering the most frequently studied combinations in the pharmaceutical-technology literature, do not exhaust the full space of emerging delivery systems (e.g., stimuli-responsive hydrogels, microneedle arrays) or modeling approaches (e.g., graph neural networks for molecular-structure-aware prediction), which represent promising areas for future comparative work as the underlying literature matures. Third, the worked example in Section 4A illustrates the mechanics of statistical model comparison using a representative, generic scenario rather than a specific published dataset, and is intended as a methodological template rather than a definitive statistical finding.

8. Conclusion

This comparative evaluation indicates that no single machine-learning algorithm is universally optimal for predicting drug release from advanced drug delivery systems; rather, the best-performing model depends systematically on the delivery-system class, dataset size, dominant release mechanism, and the relative institutional priority placed on accuracy versus interpretability versus computational cost. Ensemble tree-based methods (random forest, XGBoost)



offer a consistently favourable balance across most DDS classes and dataset sizes, deep artificial neural networks achieve the highest accuracy where sufficiently large and information-rich datasets are available (notably for liposomal and complex nanocarrier systems), and Gaussian process regression provides distinctive value for small, high-cost datasets requiring calibrated uncertainty estimates, such as implantable and reservoir devices. Realizing more reliable, cumulative comparative evidence will require the field to adopt more standardized benchmarking practices — consistent metrics, statistical significance testing, and shared or standardized datasets — so that future comparative claims can be assessed with the same analytical rigor that this paper has sought to apply to the existing literature.

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