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PREDICTING CONTROLLED-RELEASE TABLET DISSOLUTION USING POLYMER GRADE, DRUG SOLUBILITY, AND COMPRESSION PARAMETERS

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ABSTRACT

Controlled-release matrix tablets require careful balancing of polymer characteristics, drug solubility, and compression conditions to achieve a desired dissolution profile. Because these factors influence drug release through swelling, diffusion, erosion, and changes in tablet porosity, formulation development often relies on repeated experimental trials and design-of-experiments approaches. This can be time-consuming when several material and process variables interact within a large formulation space. This manuscript presents a predictive modelling approach for estimating the complete dissolution profile of controlled-release tablets using key formulation and manufacturing inputs. The proposed framework uses polymer molecular weight and viscosity, drug solubility in aqueous and buffered media, compression pressure, dwell time, and tablet porosity as model features. A gradient-boosted multi-output regression model is conceptually applied to predict percent drug released at multiple time points, with the predicted profile optionally linked to a kinetic model such as the Weibull function.

Rather than estimating only a single dissolution endpoint, the model is designed to forecast the entire release curve and provide insight into the variables that influence early, intermediate, and late release phases. Such a framework could allow polymer grade selection, solubility adjustment, and compression settings to be evaluated before tablet manufacture. Overall, this modelling strategy may reduce experimental burden, improve formulation efficiency, and support Quality-by-Design and real-time release testing. Its successful application would require transparent feature selection, mechanistically consistent curve prediction, and prospective experimental validation.

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Introduction

Dissolution testing is central to controlled-release tablet development because the release profile provides a practical link between formulation design, manufacturing conditions, and expected in vivo performance. Extended-release systems are particularly challenging because the desired profile is not only a final amount released but a time-dependent trajectory shaped by matrix hydration, gel formation, and erosion. Recent predictive dissolution studies have shown that spectroscopy-based and formulation-based models can support release-profile estimation, suggesting that dissolution data are suitable for supervised modelling when formulation and process variables are recorded consistently [1]. In this context, a controlled-release matrix tablet should be treated as a dynamic system whose dissolution behavior emerges from interacting polymer, drug, and compression attributes rather than from one isolated factor.

Traditional development relies on formulation experience, sequential prototype batches, and design-of-experiments strategies to explore polymer grades, drug loading, and compression conditions. Such workflows can generate valuable structured data, but the relationships between inputs and dissolution profiles may remain only partly exploited if they are interpreted through one-factor-at-a-time reasoning. Model-based and Quality-by-Design-oriented work on matrix tablets has highlighted how formulation variables and geometric or hydrodynamic conditions can be rationalized through predictive frameworks rather than empirical screening alone [2]. Machine learning offers a way to reuse development data by learning the mapping between

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formulation descriptors and the complete release curve, which has already been explored for dissolution prediction from spectral and process measurements [3].

Modern machine learning methods are suited to this problem because they can represent non-linear interactions between polymer properties, drug solubility, and manufacturing parameters without requiring the analyst to specify every interaction term in advance. Artificial neural networks, random decision forests, and other data-driven models have been applied to dissolution-profile prediction, including cases where the input information came from process analytical technology or spectroscopic measurements [4, 5]. These studies indicate that models can learn relationships between tablet attributes and release behavior, while also motivating a formulation-first approach in which polymer grade, solubility, and compression are explicit design variables. A predictive model for controlled-release tablets should therefore combine the flexibility of supervised learning with physicochemical features that retain mechanistic meaning.

The central thesis of this manuscript is that a machine learning model can predict the full dissolution profile of controlled-release tablets from polymer grade, drug solubility, and compression parameters, while kinetic equations can be used to regularize and interpret the predicted curve. The model is not proposed as a substitute for dissolution testing, but as a decision-support tool that could prioritize formulations and define a rational design space. Weibull, Higuchi, Korsmeyer-Peppas, and related functions remain useful because they describe release-curve shape in compact parameters that can be linked to swelling, diffusion, and erosion [6]. By combining such kinetic structure with machine learning, the model can provide both profile forecasting and mechanistic guidance for selecting polymer viscosity grade, adjusting compression force, and managing solubility-driven burst release.

Background

Mechanism of Release from Matrix Tablets

Drug release from matrix tablets is governed by coupled diffusion, swelling, erosion, and, in some systems, relaxation of the polymer network after hydration. Kinetic models such as the Weibull function are widely used because they can describe sigmoidal or stretched release behavior with interpretable scale and shape parameters [7]. Comparative work on Weibull and fractional kinetic functions has shown that the choice of model affects how release mechanisms are inferred from dissolution data [6]. For predictive modelling, these equations are useful not because they capture every microscopic event, but because they impose physically plausible curve shapes that can guide machine learning outputs.

Polymer Grade and Its Influence on Release

Polymer grade influences controlled release through molecular weight, viscosity, substitution chemistry, hydration rate, and the mechanical strength of the gel layer formed at the tablet surface. Hydroxypropyl methylcellulose matrix studies have shown that polymer-controlled hydrodynamic changes can govern drug release and matrix behavior, making viscosity grade a meaningful predictive descriptor rather than a simple label [8]. Work on HPMC-based systems has also demonstrated that changing polymer grade or lipidic matrix components can alter release and rheological behavior, supporting the use of polymer properties as continuous input features [9]. Similarly, polyethylene oxide matrix tablets show swelling evolution that depends on molecular mass and tablet composition, reinforcing the need to encode polymer grade through measurable physical attributes [10].

Drug Solubility and Compression Parameters

Drug solubility shapes the early and intermediate phases of release by influencing concentration gradients, burst release, and the rate at which dissolved drug can diffuse through the hydrated matrix. Compression parameters act through a different but coupled pathway, because higher compaction changes tablet porosity, hardness, and water penetration, which in turn alters dissolution kinetics. Studies using optical porosity measurements to predict dissolution and tablet hardness support the idea that compression-derived structure can serve as a predictive input for release modelling [11]. Real-time release testing studies that incorporated compression force alongside spectroscopic and particle-size information further indicate that process variables can improve dissolution prediction when they are integrated into the modelling framework [12].

Machine Learning in Dissolution and Formulation Science

Machine learning has already been applied to dissolution prediction using artificial neural networks, random forests, convolutional neural networks, and other flexible regression approaches. Spectroscopy-based studies have predicted extended-release dissolution profiles using artificial neural networks, showing that data-driven models can connect measured tablet attributes to release curves [3]. Raman mapping and fast Raman imaging have also been used with predictive models to estimate sustained-release tablet dissolution, suggesting that spatial chemical information can support full-profile prediction [13, 14]. However, a remaining gap is the development of formulation-first models that predict dissolution from polymer grade, drug solubility, and compression parameters without requiring specialized spectroscopic imaging for every candidate formulation.

Quality-by-Design and Predictive Dissolution Models

Quality-by-Design requires a rational understanding of how material attributes and process parameters influence critical quality attributes such as dissolution. Predictive dissolution models can support this objective by linking polymer grade,

solubility, porosity, and compression settings to the probability of meeting a target release profile. Continuous manufacturing and real-time release studies have shown that model predictive dissolution testing can be integrated into pharmaceutical process control concepts [15]. A model that incorporates kinetic constraints and interpretable feature effects would therefore be expected to support both formulation design and regulatory communication more effectively than a purely black-box prediction.

Model Development Overview

High-Level Prediction Framework

The proposed framework accepts formulation and process descriptors as inputs and returns the predicted percentage of drug released at standard dissolution sampling times. Polymer grade is represented by molecular and hydration-related variables, drug behavior is represented by aqueous and pH-buffered solubility descriptors, and compression is represented by force, dwell time, and porosity-related features. Multi-output prediction is appropriate because dissolution is a curve-valued response rather than an isolated endpoint, an approach consistent with studies that directly model full release profiles rather than only a single time point [16]. The model output can be used to compare candidate formulations against a target profile before selecting batches for experimental confirmation.

Figure 1 presents the proposed end-to-end predictive modeling workflow linking polymer-grade descriptors, drug-solubility attributes, and compression-derived structural features to full dissolution-profile prediction and Quality-by-Design decision support.

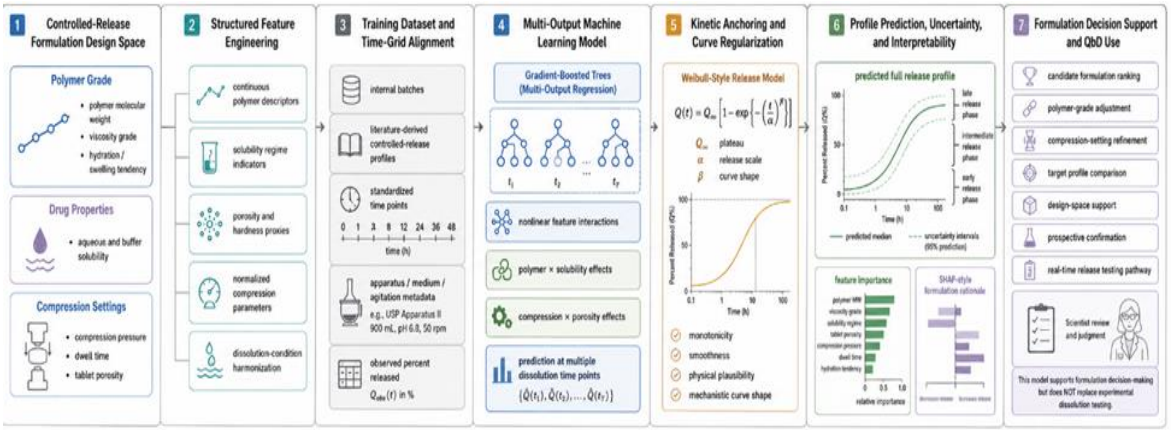

Figure 1. Predictive Modeling Workflow for Controlled-Release Tablet Dissolution Using Polymer Grade, Drug Solubility, and Compression Parameters

Core Input Features

The core polymer inputs include molecular weight, viscosity grade, hydrophilicity, and swelling or erosion-related descriptors that approximate gel-layer formation. Drug inputs include solubility in water and physiologically relevant buffer, because pH-dependent solubility can shift the balance between diffusion-limited and solubility-limited release. Process inputs include compression force, dwell time, and calculated tablet porosity, which capture the structure through which dissolution medium must penetrate. Data-driven dissolution studies using raw material databases and machine learning support the feasibility of using structured formulation descriptors as predictive inputs rather than relying solely on post-manufacture analytical spectra [17].

Design Principles

The model is designed around four principles: multi-time-point prediction, physicochemical feature encoding, kinetic anchoring, and interpretability. Multi-output regression captures the temporal dependence of dissolution, while feature encoding ensures that polymer grade and solubility are represented as continuous variables that can support interpolation. Kinetic anchoring is motivated by studies showing that functions such as Weibull can carry mechanistic information about release-curve shape and release mechanism. Interpretability methods such as feature importance or SHAP-style reasoning would then help formulators connect predicted changes in dissolution to polymer viscosity, solubility, and compaction state.

Data Sources and Feature Engineering

Curation of Controlled-Release Formulation Datasets

A controlled-release dissolution dataset for this model would be curated from internal development reports and peer-reviewed formulation studies, provided that dissolution conditions, sampling times, formulation composition, and compression parameters are recorded consistently. Literature-derived model development should harmonize release measurements across apparatus type, medium, agitation, and time grid to avoid learning differences caused only by testing conditions. Previous

work comparing data-driven approaches for extended-release matrix tablets illustrates how dissolution datasets can be structured for model training and profile prediction [18]. The curated dataset should therefore be treated as a formulation-development knowledge base rather than as a collection of unrelated dissolution curves.

Encoding Polymer Grade and Drug Solubility

Polymer grade should be encoded through measured or supplier-reported continuous properties such as molecular weight, nominal viscosity, substitution pattern, hydrophilicity, and swelling tendency. Encoding polymer type as a categorical name alone would limit interpolation to new grades, whereas continuous descriptors allow the model to learn trends across related excipient families. Drug solubility should likewise be represented using measured values in water and relevant buffer media, because rational dissolution prediction depends on whether release is dominated by solubility, diffusion, or matrix erosion. Biorelevant dissolution modelling that combines experimental apparatus, design of experiments, and machine learning reinforces the importance of encoding formulation variables in a way that reflects the environment experienced by the dosage form [19].

Deriving Compression-Related Features

Compression-related features translate manufacturing settings into structural descriptors that influence water ingress and drug diffusion. Compression force and dwell time should be recorded directly from press instrumentation, while porosity can be estimated from tablet mass, true density, and tablet dimensions. Tablet hardness can be included as an indirect compaction descriptor, although it should not replace porosity when structural interpretation is needed. Near-infrared prediction of dissolution and hardness from tablet attributes supports the idea that compaction-derived features can carry information relevant to both mechanical integrity and release behavior [20]. **Figure 2** summarizes the proposed design-principle and feature-engineering architecture linking curated dissolution data, continuous physicochemical descriptors, compression-derived structural variables, kinetic anchoring, and interpretable multi-time-point prediction.

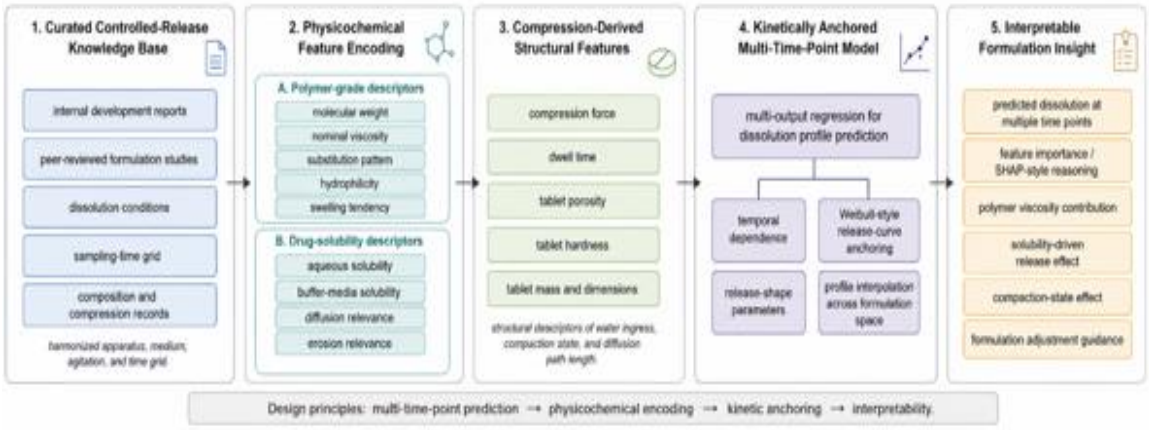

Figure 2. Design-principle and feature-engineering architecture for controlled-release dissolution prediction, showing how curated dissolution datasets, physicochemical descriptors, compression-derived structural features, kinetic anchoring, and interpretability are integrated into a multi-time-point predictive model.

Table 1 organizes the proposed predictor variables according to the release mechanisms they represent, clarifying how polymer grade, drug solubility, compression intensity, and structural tablet attributes contribute differently across early, intermediate, and late dissolution phases.

Table 1. Mechanistic Feature-to-Release Mapping for Predicting Controlled-Release Tablet Dissolution Profiles

Feature domain	Specific model-ready variables	Mechanistic release pathway represented	Expected influence on dissolution profile	Most relevant release phase	Modeling implication
Polymer molecular properties	Molecular weight, nominal viscosity grade, substitution pattern, hydrophilicity	Controls gel-layer formation, polymer-chain relaxation, diffusional resistance, and erosion behavior	Higher molecular weight or viscosity generally slows water penetration and drug diffusion by strengthening the hydrated matrix	Intermediate to late phase	Should be encoded as continuous descriptors rather than only as polymer names to support interpolation across grades
Polymer hydration behavior	Swelling index, erosion tendency, hydration rate, gel strength proxy	Represents the transition from dry compact to hydrated matrix barrier	Faster hydration may reduce burst release, while weak gel formation may increase early release or erosion-driven variability	Early to intermediate phase	Supports mechanistic interpretation of curve shape and Weibull β behavior

Drug solubility profile	Aqueous solubility, pH-buffered solubility, solubility class, pH-dependent solubility ratio	Defines concentration gradient and drug availability for diffusion through the matrix	Highly soluble drugs may show greater early release pressure; poorly soluble drugs may show dissolution-limited release	Early to intermediate phase	Should be modeled jointly with polymer viscosity because solubility effects depend on matrix resistance
Compression intensity	Compression force, compaction pressure, dwell time	Determines tablet densification, pore collapse, and mechanical resistance to medium penetration	Higher compression may reduce porosity and slow early water ingress, but excessive compaction may alter matrix relaxation	Early phase and onset of intermediate phase	Should interact with porosity and hardness features rather than be treated as an isolated process setting
Tablet structural attributes	Porosity, hardness, tensile strength, dimensions, density	Represents physical pathways for dissolution medium penetration and drug diffusion	Lower porosity may delay hydration and reduce burst release; higher porosity may accelerate medium uptake	Early phase	Porosity should be prioritized over hardness alone when mechanistic interpretation is required
Dissolution-test conditions	Medium pH, apparatus, agitation rate, sampling grid, temperature	Captures external hydrodynamic and environmental drivers of release	Different media or agitation conditions can shift apparent release kinetics independent of formulation design	All phases	Must be harmonized or included as metadata to prevent the model from learning test-condition artifacts
Kinetic curve descriptors	Weibull Q_∞, α, β; optional Higuchi or Korsmeyer-Peppas parameters	Provides compact shape representation of release trajectory	α reflects release timescale, β reflects curve shape, and Q_∞ reflects plateau extent	Full profile	Enables physically plausible curve prediction and connects machine-learning output to dissolution theory
Profile-level targets	Percent released at multiple time points, target-profile deviation, f_2 similarity	Treats dissolution as a temporal trajectory rather than a single endpoint	Allows detection of early burst, delayed release, incomplete release, or profile-shape mismatch	Full profile	Multi-output or curve-parameter prediction is preferable to single-time-point regression

Predictive Model Architecture

Multi-Output Regression Model

A gradient-boosted tree model can be configured as a multi-output regressor to predict the percentage released at each dissolution sampling time, while an alternative neural network can learn a time-constrained release curve from the same formulation features. Gradient boosting is attractive for tabular formulation datasets because it can represent non-linear interactions among polymer viscosity, drug solubility, and compression-derived porosity without requiring explicit preselection of interaction terms. Neural network approaches are also plausible because prior dissolution studies have used artificial neural networks for profile prediction and process analytical technology applications [4]. The architecture should be selected not by claimed superiority in advance, but by how well it supports curve consistency, interpretability, and prospective formulation decisions.

Anchoring Predictions to a Kinetic Model

Instead of predicting each release time point independently, the model can predict parameters of a Weibull release function,

$$Q(t) = Q_\infty \left(1 - \exp\left[-\left(\frac{t}{a}\right)^{\beta}\right]\right) \quad (1)$$

where (Q(t)) is the predicted percent released at time (t), (Q_∞) is the plateau release, (a) is a scale parameter, and (\beta) is a shape parameter. In this formulation, (a) and (β) would be learned as functions of polymer grade, drug solubility, and compression features, allowing the model to connect formulation variables to release-curve shape. The Weibull equation is appropriate because its fitted parameters have been discussed in relation to diffusion-controlled release and mechanistic interpretation [7]. This kinetic anchoring reduces the chance of physically implausible non-monotonic predictions and aligns the machine learning task with established dissolution modelling practice.

Training and Regularization

The training objective would minimize the discrepancy between predicted and observed dissolution profiles while discouraging release curves that violate expected monotonicity or kinetic smoothness. When the model predicts Weibull parameters rather than raw time points, regularization is partly imposed through the kinetic form itself, because all predicted time points are generated from a compact set of curve parameters. Constrained neural-network approaches for dissolution slowdown modelling illustrate how machine learning can be shaped by formulation-relevant assumptions rather than used as an unconstrained black box [21]. Model development should also compare surrogate-model behavior using profile-level evaluation logic, since dissolution prediction must preserve the entire curve rather than only individual sampling values [22].

Handling Temporal Dissolution Data and Profile Comparison

Multi-Time-Point Prediction and Correlation

Dissolution profiles contain temporal correlation because the release observed at one sampling time constrains the physically plausible release at later times. A profile-aware loss function should therefore evaluate the whole curve rather than treating each time point as an independent scalar response. Similarity-based comparison can be included conceptually through the (f_2) similarity factor, which penalizes profile-level differences and is often discussed when predicted and reference dissolution curves are compared. Comparative work on surrogate models for dissolution prediction emphasizes that profile-level evaluation is important because an apparently acceptable pointwise fit may still distort the overall release trajectory [22].

Predicting the Entire Profile for a New Polymer Drug Combination

For a new polymer-drug combination, the model would accept continuous descriptors such as polymer viscosity, molecular weight, drug solubility, and compression-derived porosity, then generate a predicted release curve over the dissolution time grid. This approach is expected to support interpolation across related polymer grades more effectively than a categorical formulation label, provided that the new formulation lies within the learned chemical and process space. Prediction from bilayer tablets using non-destructive near-infrared spectroscopy demonstrates that dissolution profiles can be inferred from structured tablet information when relevant tablet attributes are captured [23]. Similarly, three-dimensional printed tablet work shows that density and release can be linked through predictive measurements, reinforcing the value of structural descriptors for release-profile estimation [24].

Assessing Prediction Uncertainty

Prediction uncertainty should be reported conceptually as intervals around the expected release curve, allowing formulators to judge whether a candidate tablet is likely to remain within a target dissolution window. Bootstrapped tree ensembles, quantile regression, or Bayesian-style neural networks could provide uncertainty bands at each time point without implying that a single predicted curve is definitive. Mathematical reviews of dissolution testing and real-time release testing highlight that model-based dissolution decisions require attention to uncertainty, model scope, and the assumptions connecting measurement to release behavior [25]. Uncertainty estimates are especially important when the model is used to extrapolate toward new polymer grades, solubility regimes, or compression settings.

Model Interpretability and Formulation Rationalization

Global Feature Importance and SHAP Analysis

Global interpretability would identify which formulation and process variables most influence predicted release across the design space. For example, polymer viscosity would be expected to dominate later dissolution phases by controlling gel strength and diffusional resistance, whereas drug solubility could have a stronger influence on early release from the hydrated matrix. Swelling and erosion studies of extended-release mirabegron tablets show that release dynamics can be rationalized through hydration, swelling, and erosion mechanisms, which are the same types of mechanisms that interpretable model outputs should recover [26]. Feature-importance or SHAP-style analysis would therefore be used not simply to rank variables, but to test whether the learned model is consistent with matrix-release theory.

Translating Model Logic into Formulation Guidance

Model interpretation becomes useful when it can be translated into formulation actions such as increasing polymer viscosity, reducing soluble drug exposure at the tablet surface, or adjusting compression to reduce porosity. If the predicted Weibull shape suggests excessively rapid initial release, the model could indicate that a higher-viscosity polymer grade or a higher compaction setting would be expected to reduce burst behavior. Raman mapping-based dissolution prediction shows how model outputs can be linked back to spatial or material drivers of release, supporting the broader principle that prediction should be accompanied by mechanistic rationalization [13]. The goal is not to let the model automatically prescribe a formulation, but to guide scientific decisions that remain subject to formulation judgment and confirmatory testing.

Integration into Formulation Development and QbD

Rapid Screening of Formulation Candidates

In development use, the model could be implemented as a screening tool in which formulators enter polymer properties, drug solubility values, and compression settings to obtain a predicted dissolution profile. This would allow candidate formulations to be ranked before tablet manufacture, reducing the number of low-probability experimental batches. Real-time release testing studies using spectroscopy, compression force, and particle-size information demonstrate how predictive dissolution models can be connected to practical manufacturing and release-decision workflows [12]. Machine-vision-based dissolution prediction further suggests that predictive tools can complement conventional dissolution testing by providing early release-behavior estimates from tablet attributes [27].

Supporting Regulatory Flexibility

Within a Quality-by-Design framework, the model could support design-space definition by mapping combinations of polymer grade, solubility, and compression conditions to predicted dissolution acceptability. Rather than presenting the algorithm as a

black box, the development package should explain how inputs relate to release mechanisms and how kinetic anchoring constrains the predicted profile. Continuous powder-blending work combining near-infrared spectroscopy and machine vision illustrates how real-time release testing concepts can be integrated with broader process understanding [28]. A predictive model with interpretable drivers would therefore be expected to support regulatory flexibility only when its domain, assumptions, and validation strategy are clearly justified.

Evaluation Strategy

Predictive Accuracy

Predictive accuracy should be evaluated at the level of individual time points and at the level of the full dissolution profile. Root mean squared error can be used conceptually to summarize pointwise deviations, while the (f_2) similarity factor can be used to describe whether the predicted and observed curves are similar as profiles. Dissolution-model reviews emphasize that kinetic and similarity-based metrics answer different questions, so both should be considered when evaluating a release-profile predictor [25]. The evaluation should avoid relying on one numerical endpoint because a model could appear adequate at a late time point while misrepresenting early burst or intermediate release. **Table 2** summarizes the proposed metrics for evaluating predictive accuracy at individual dissolution time points and across the complete release profile.

Table 2. Evaluation metrics for assessing predictive accuracy of dissolution-profile modelling

Evaluation Aspect	Purpose	Suggested Metric	What It Shows	Key Consideration
Individual time-point accuracy	To assess prediction error at each dissolution sampling time	Root mean squared error (RMSE)	Measures the average deviation between predicted and observed drug release values at specific time points	Useful for identifying errors in early, intermediate, or late release phases
Full dissolution-profile similarity	To compare the overall predicted and observed release curves	Similarity factor	Indicates whether the predicted and observed dissolution profiles are similar as complete curves	Complements pointwise error metrics by evaluating profile-level agreement
Kinetic-model agreement	To assess whether the predicted curve follows plausible release behavior	Kinetic model fitting, such as Weibull-based comparison	Shows whether predicted release is mechanistically and mathematically consistent	Important because a curve may have acceptable errors but unrealistic release kinetics
Phase-specific performance	To evaluate different stages of drug release	RMSE or absolute error by release phase	Identifies whether the model captures early burst, intermediate diffusion, and late-stage release	Prevents overreliance on a single late endpoint
Overall model adequacy	To judge whether the model is suitable for formulation prediction	Combined use of RMSE, and kinetic interpretation	Provides a balanced assessment of numerical accuracy and dissolution-profile similarity	A model should not be accepted based on one endpoint alone

Temporal and Formulation-Based Validation

Validation should withhold entire polymer-drug combinations rather than randomly splitting individual tablets from the same formulation across training and testing sets. This strategy better reflects the intended use case, where the model is asked to generalize to a new formulation rather than reproduce measurements from a near-duplicate batch. External validation can use literature-derived extended-release formulations when dissolution conditions and formulation descriptors are sufficiently harmonized, as shown by comparative data-driven studies of extended-release matrix tablet modelling [18]. The validation plan should therefore test temporal curve prediction, formulation extrapolation, and sensitivity to differences in dissolution method.

Prospective Experimental Testing

Prospective testing would involve selecting a small set of candidate formulations or compression settings suggested by the model and then comparing measured dissolution profiles against the predicted curves. These verification batches would not be presented as proof of universal model validity, but as evidence that the model can support real formulation decisions within its defined scope. Model predictive dissolution testing in continuous manufacturing demonstrates how prospective comparisons between predicted and measured dissolution behavior can be framed as part of process and product understanding [15]. The strongest evaluation strategy would combine retrospective validation, external literature checks, and prospective confirmation under standardized dissolution conditions.

Table 3 consolidates the proposed model architecture, validation logic, uncertainty strategy, interpretability requirements, and Quality-by-Design decision-use conditions needed for a controlled-release dissolution predictor to function as a credible formulation-development tool.

Table 3. Model Architecture, Validation, and Decision-Use Framework for Controlled-Release Dissolution Prediction

Analytical layer	Core function in the proposed framework	Recommended implementation	Main risk if omitted or weakly specified	Evaluation criterion	Formulation-development value
Feature-domain definition	Establishes the formulation and process space from which predictions are valid	Define polymer family, viscosity range, solubility range, compression range, porosity range, and dissolution-test conditions	Model may be applied outside its learned formulation domain	Applicability-domain assessment; out-of-range feature flagging	Prevents overconfident prediction for unfamiliar polymers, drugs, or compaction states
Multi-output profile prediction	Predicts percent released across the entire dissolution time grid	Use gradient-boosted multi-output regression or a constrained neural model	A single endpoint may hide burst release, delayed release, or intermediate-profile failure	Time-point RMSE / MAE plus profile-level error	Supports formulation decisions based on complete release trajectory
Kinetic anchoring	Regularizes model output using release-curve structure	Predict Weibull parameters Q_∞, α, and β, or fit predicted time points to a kinetic curve	Independent time-point predictions may become non-monotonic or physically implausible	Monotonicity, smoothness, kinetic-parameter plausibility	Links prediction to established dissolution theory and improves regulatory explainability
Interaction modeling	Captures nonlinear relationships between polymer, drug, and process variables	Model polymer viscosity × solubility, solubility × porosity, and compression × hydration interactions	Important release behavior may be falsely attributed to one isolated factor	Interaction importance; partial-dependence or SHAP interaction patterns	Reveals formulation trade-offs that conventional one-factor reasoning may miss
Uncertainty estimation	Communicates prediction reliability around the expected release curve	Use bootstrapped ensembles, quantile regression, or Bayesian-style uncertainty bands	Candidate formulations may be selected based on overly precise point predictions	Coverage of uncertainty intervals; calibration of predicted bands	Helps prioritize formulations with acceptable predicted performance and acceptable uncertainty
Interpretability layer	Converts model behavior into formulation rationale	Use global feature importance, phase-specific attribution, and SHAP-style analysis	Model may become a black-box screening tool with limited scientific credibility	Consistency between attribution patterns and matrix-release theory	Guides practical actions such as changing polymer grade, compression force, or solubility-management strategy
Validation design	Tests generalization to genuinely new formulations	Withhold entire polymer-drug combinations; perform temporal and formulation-based validation	Random splits may exaggerate performance by leaking near-duplicate formulation information	External validation, formulation-holdout performance, f_2 similarity	Demonstrates whether the model can support new formulation decisions
Prospective confirmation	Tests whether model-guided decisions work experimentally	Manufacture selected candidate tablets and compare measured versus predicted profiles	Retrospective accuracy may not translate into real development utility	Predicted-versus-observed profile agreement under standardized testing	Provides practical evidence for formulation screening and QbD design-space support
QbD integration	Connects prediction to development and regulatory use	Map input ranges to predicted dissolution acceptability and define model-supported design space	Model remains a research exercise rather than a decision-support framework	Target-profile attainment, design-space robustness, documented assumptions	Supports rational formulation selection, reduced experimental burden, and potential real-time release testing pathways

Limitations

Data Sparsity and Scope

A key limitation is that the model would only be reliable within the polymer chemistries, solubility ranges, and compression conditions represented in the training data. Predictions for a completely new excipient chemistry, an unusual swelling mechanism, or a drug with atypical pH-dependent solubility may be unreliable without calibration data. Polyethylene oxide swelling studies illustrate how polymer molecular mass and composition can produce specific matrix behaviors that may not transfer directly to other polymer families [10]. The model should therefore define its applicability domain explicitly and flag formulations that fall outside the learned feature space.

Neglect of Storage Condition and Stability Effects

The proposed model predicts dissolution for freshly prepared or development-stage tablets and does not explicitly account for long-term storage effects. Moisture uptake, physical aging, polymer relaxation, drug recrystallization, or changes in tablet hardness could alter release behavior after manufacture. Studies linking tablet porosity, hardness, and dissolution prediction

show that structural attributes are important to release behavior, which implies that storage-induced structural change could affect model validity if not included as an input [11]. Future versions of the model should therefore incorporate stability-condition descriptors when aged-batch dissolution data become available.

Conclusion

A machine learning model for controlled-release tablet dissolution can be framed as a profile predictor that maps polymer grade, drug solubility, and compression parameters to the expected percent released over time. By treating dissolution as a curve-valued response, the model supports formulation decisions that depend on the shape of release rather than on a single sampling point.

The main strength of the proposed approach is the combination of flexible supervised learning with kinetic structure. A Weibull-anchored architecture can regularize the predicted curve, improve physical plausibility, and allow parameters such as release scale and shape to be interpreted in relation to formulation variables. Interpretability methods can then translate model behavior into practical guidance for polymer selection and compression adjustment.

Important challenges remain. The model would require sufficient chemical and process diversity to support credible interpolation, and its predictions would be weaker for new polymer chemistries or stability-related changes not represented in training. Prospective validation would also be essential before the model could be used to support development or release-related decisions.

Progress in this area would benefit from collaboration between industrial formulation scientists and academic groups. Open, standardized dissolution datasets containing formulation descriptors, polymer-grade information, solubility measurements, compression parameters, and full release profiles would accelerate the development of reliable predictive formulation models.

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