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Quality by Design (QbD) Framework for Manufacturing Peptide-Drug Conjugates

Mohammad Ali Riaz

Ph.D, Blue Marble University, Roseau 00152, Commonwealth of Dominica
Corresponding Author Email: *riazmohammadali[at]gmail.com*

Abstract: ***A unified computational Quality by Design framework integrates kinetic modelling, computational fluid dynamics, and interpretable machine learning to define a risk-based design space for peptide drug conjugate manufacturing. The kinetic model, parameterized from aggregated literature, yields an activation energy of 52 kJ mol⁻¹ for maleimide cysteine conjugation and reproduces observed rates of 0.5 L mol⁻¹ min⁻¹ at 25 °C and pH 7.4, enabling prediction of conversion times where 98% conversion is reached in roughly 18 minutes at pH 7.4 compared to roughly 40 minutes at pH 6.5, and aggregated degradation behavior with a combined half-life of approximately 14 hours at pH 7.4 and 37 °C. CFD simulations of a microfluidic T mixer with 200 µm channels report mixing indices exceeding 0.95 within milliseconds, reaching 0.95 in 2.3 ms at 50 µL min⁻¹, and Damköhler numbers remaining below 0.1 with a maximum of approximately 0.08 for flow rates up to 500 µL min⁻¹, supporting a numbering up scale up strategy while noting Newtonian and boundary condition assumptions. An XGBoost surrogate trained on literature formulation data predicts PLGA microsphere particle size and encapsulation efficiency with RMSE values near 12 nm and 3.5%, respectively, and SHAP analysis ranks sonication amplitude with a mean SHAP value of approximately 14.2 nm and polymer concentration with a mean SHAP value of approximately 9.5 nm as dominant drivers. These mechanistic and data driven outputs are mapped to ICH Q8 through Q10 concepts to set allowable ranges for temperature, reaction time, flow rate, sonication energy, and polymer concentration, and to specify PAT and SPC strategies for lifecycle management. Limitations and targeted next steps including bench kinetics, pilot mixing validation, PAT deployment, and incremental ML retraining are identified to reduce uncertainty and enable regulatory engagement.***

Keywords: Quality by Design, peptide drug conjugates, maleimide thiol conjugation, multi pathway kinetics, computational fluid dynamics, XGBoost, SHAP, ICH Q8, process analytical technology, design space

1. Introduction

Targeted anticancer bioconjugates have progressed from Ehrlich's magic bullet to clinically relevant antibody drug conjugates, but the size and manufacturing complexity of antibody drug conjugates limit solid tumor penetration and raise costs. Peptide drug conjugates offer a smaller, synthetically simpler alternative whose performance depends critically on the chemical integrity of the peptide payload linkage. Maleimide thiol conjugation, while convenient, yields a Thio succinimide adduct that behaves as a kinetic intermediate subject to at least three competing first order degradation pathways: retro Michael addition, thiol exchange with endogenous nucleophiles, and ring opening hydrolysis or ammonolysis. Thiol exchange is especially consequential because plasma thiols can transfer payloads to off target carrier proteins during manufacture, storage, and after administration, directly undermining targeted delivery. Ensuring linker stability is therefore a critical quality requirement [1], [2].

Quantitative prediction of conjugation yield and product evolution requires explicit multi pathway kinetic models rather than a single apparent rate. Such mechanistic descriptions have been emphasized in recent kinetic studies and reviews [2], [3]. These models are conveniently parameterized by first order or pseudo first order rate constants and may be informed by parameter estimation approaches including nonlinear least squares, maximum likelihood, and Bayesian inference. Bayesian methods are valuable when data are sparse because they quantify parameter uncertainty for downstream risk analysis [2], [3]. Molecular modelling and molecular dynamics can supply activation energies for Arrhenius type scaling and provide mechanistic hypotheses to guide experiments. In this work the conjugation activation energy is taken to be approximately 52 kJ mol⁻¹, a system dependent value that should be treated with appropriate uncertainty [2].

Scale up compounds chemical fragility with transport and mixing effects. Maleimide thiol reactivity is sensitive to temperature, pH, and residence time. Optimal reactivity occurs near pH 6.5 to 7.5, a window that also permits competing hydrolysis and exchange. Whether a spatially lumped kinetic model applies depends on the Damköhler number, defined as the ratio of mixing time to reaction time. Values greater than unity imply mixing limited, spatially heterogeneous chemistry and higher by product formation, whereas values well below unity justify kinetically controlled, homogenized operation [1], [4]. CFD of a prototype T mixer here indicates Damköhler numbers below 0.1 up to 500 µL min⁻¹, supporting a numbering up strategy that preserves favorable mixing. These CFD conclusions, however, assume Newtonian behavior, accurate boundary conditions, and negligible concentration dependent on viscosity or interfacial phenomena and therefore require experimental corroboration when nonidealities such as high solids loading or emulsification are plausible [1], [4].

Downstream formulation, illustrated by PLGA microspheres, adds high dimensional process variability and well documented formulation sensitivities [3], [4]. To navigate this space efficiently, this work integrates literature datasets with machine learning. An XGBoost model predicts critical quality attributes such as particle size and encapsulation efficiency, and SHAP analysis ranks input influence, identifying sonication amplitude and polymer concentration as high-risk critical process parameters [3],

[4]. Practically, this prioritizes real time sensors and SPC metrics. Process capability indices and control charts can demonstrate stable operation within limits [1], [2]. Combining these formulation limits with conjugation step boundaries derived from kinetic models yields a multidimensional design space consistent with ICH Q8 expectations [1].

The result is an integrated computational QbD framework that synthesizes published data, mechanistic kinetics, CFD mixing analysis, and data driven formulation optimization to prioritize experiments that most reduce uncertainty, recommend scale up tactics that preserve kinetically controlled conditions such as numbering up when the Damköhler number is well below unity, and identify critical process parameters that require stringent monitoring and control. This QbD oriented lifecycle perspective aligns with broader ICH expectations including Q8 through Q10 principles and lifecycle management and supports continuous process verification and improvement [1], [2]. Key limitations are explicit and concise. Kinetic parameters and activation energies are system dependent on peptide sequence, payload chemistry, and matrix. CFD and Damköhler number estimates depend on accurate rheological and boundary condition inputs. Machine learning models inherit training data biases and may not extrapolate reliably [2], [3]. Consequently, the proposed design space should be interpreted probabilistically and validated by targeted experiments and stability studies under relevant storage and biological conditions [3], [4].

By aligning mechanistic and data driven results with ICH Q8 through Q10 principles and embedding real time monitoring and SPC into the control strategy, this work provides a reusable, risk-based template for developing a control strategy and probabilistic design space for a model peptide drug conjugate product [1], [2]. The purpose of this paper is to present an integrated, risk-based Quality by Design framework for the manufacturing of peptide drug conjugates, combining mechanistic kinetic modeling, computational fluid dynamics, and interpretable machine learning.

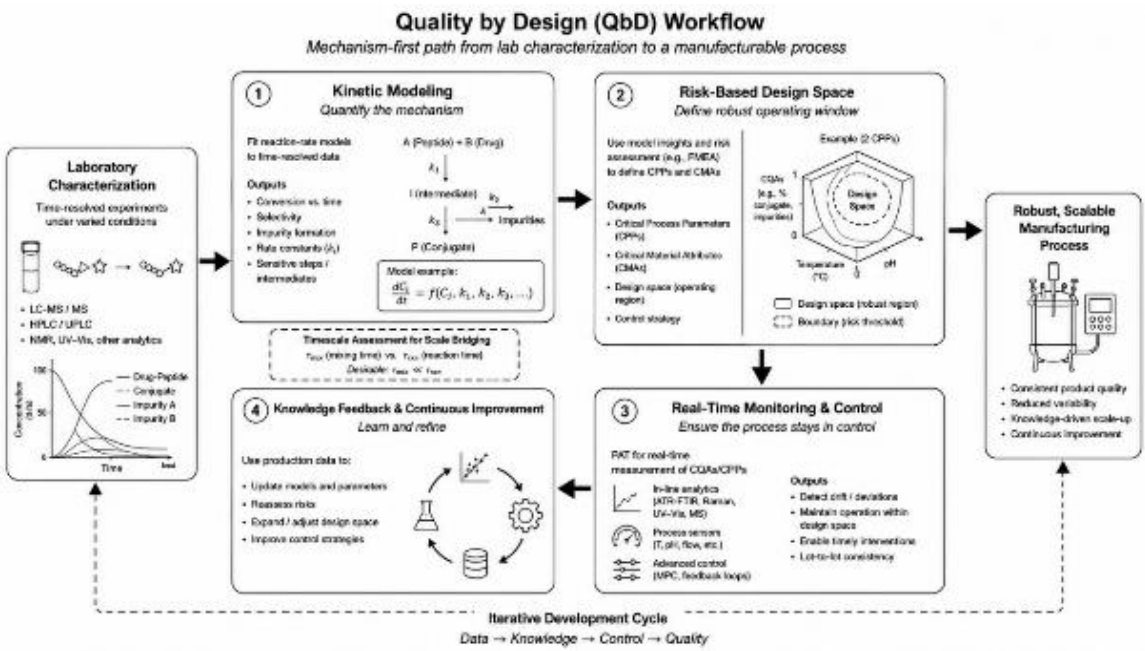

Figure 1: Schematic of the Quality by Design workflow used in this study. The schematic links laboratory characterization, kinetic model development, risk-based design-space definition, and real-time monitoring/control into an iterative development cycle for peptide–drug conjugate manufacture

2. Methods

A mechanistic kinetic model was constructed to represent the maleimide thiol conjugation reaction as a system of parallel pathways rather than collapsing distinct processes into a single apparent rate. The model resolves three competing reactions. The first is productive conjugation, yielding the Thio succinimide linked peptide drug conjugate. The second is retro Michael addition, regenerating free maleimide and thiol. The third is ring opening hydrolysis or ammonolysis, producing open chain isomers with unpredictable biological activity. Separate rate constants were assigned to each pathway to preserve mechanistic detail and avoid bias [3], [4].

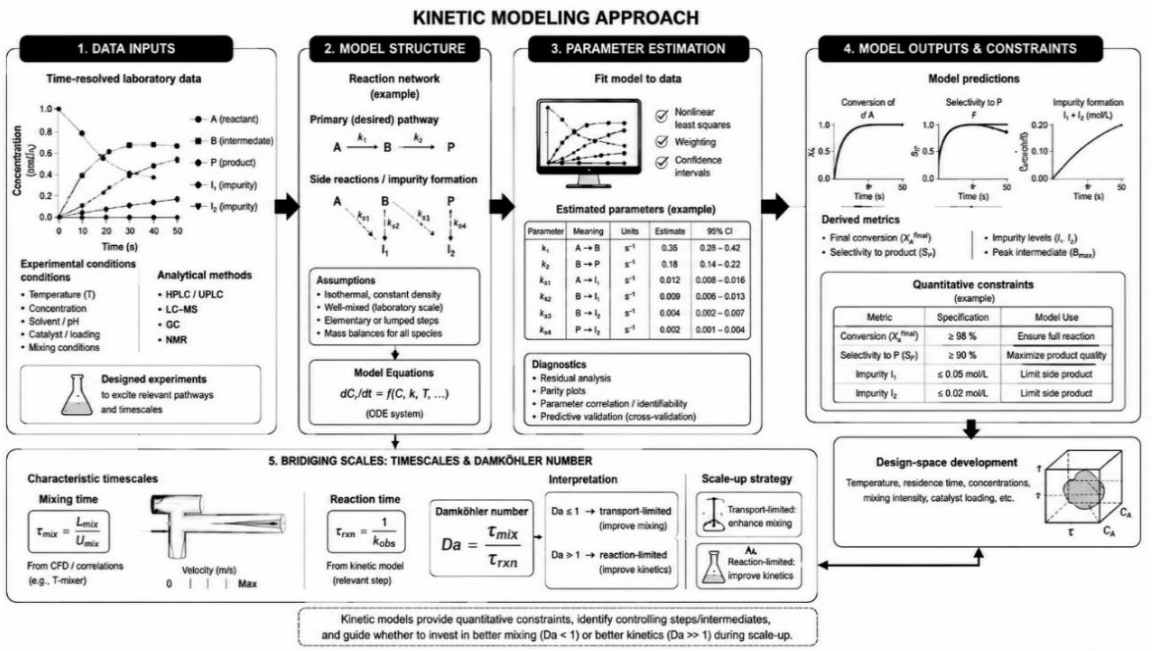

Figure 2: Schematic of the kinetic modelling approach. The diagram summarizes data input, model structure (primary and side reactions), parameter estimation, and model outputs used to derive conversion, selectivity, and impurity formation constraints for design-space development

Reactivity modifiers such as pH and temperature were included explicitly because they alter mechanism and protonation state. Maleimide thiol conjugation is optimal near pH 6.5 to 7.5 because thiol deprotonation controls nucleophilicity [4]. Temperature dependence was represented by the Arrhenius relationship, though practitioners should be cautious about Arrhenius extrapolation when mechanisms, buffer catalysis, or phase behavior change with temperature [2].

Kinetic parameters were estimated by fitting the model to published time resolved data using nonlinear least squares regression. Fitting the Arrhenius equation to published rate measurements, including the work of Knight on maleimide cysteine conjugation, yielded an activation energy of approximately 52 kJ mol^{-1} for the forward reaction. The effective second order rate constant was adjusted by the calculated thiolate fraction based on the Henderson Hasselbalch equation, using a cysteine pK_a of approximately 8.3. At pH 7.4 and 25 °C the second order rate constant is approximately 0.5 L mol^{-1} min^{-1}. The combined degradation half-life was modelled as the harmonic sum of the individual half-lives for each degradation pathway. Parameter estimation determines predictive confidence. When data are scarce or uncertainty quantification will guide control strategies, Bayesian methods are favored because they produce posterior distributions and naturally encode priors from theory or computation [3], [4]. Model selection and identifiability analyses, conducted via information criteria or profile likelihoods, expose non-identifiable parameters. When identifiability is poor, targeted experiments such as pulse chase or isotopic labelling can recover pathway specific information [3]. Atomistic calculations and molecular simulation complement macroscopic kinetics. Quantum chemistry and transition state theory can provide estimates of activation energies and pre-exponential factors, while molecular dynamics can reveal steric or conformational constraints [2], [4]. These outputs should be used as priors or constraints in kinetic fits rather than as replacements for calibration [2].

A three-dimensional CFD model of a T mixer microfluidic geometry with square channels of 200 µm side length was constructed using Open FOAM. The model solved the steady state Navier Stokes equations for an incompressible Newtonian fluid with species transport for a passive scalar representing the conjugation reactant mixture. Simulations were conducted across flow rates of 50, 200, and 500 µL min^{-1}. The mixing index, a dimensionless measure of composition uniformity, was computed from the scalar variance decay. Characteristic mixing times were extracted as the time required for the mixing index to reach 0.95. The Damköhler number was computed as the ratio of characteristic mixing time to characteristic reaction time, with the reaction time derived from the kinetic model at 25 °C and relevant concentration conditions. Explicit model assumptions and scale limitations were documented. Typical kinetic models assume well mixed, isothermal reactors with uniform activities. Real systems may exhibit concentration or pH gradients, nonideal mixing, surface adsorption, or shear effects [4]. For particulate formulations such as PLGA microspheres, surface adsorption, polymer erosion, and heterogeneous transport introduce additional mechanistic pathways that must be represented explicitly in multi pathway kinetics [3], [4]. Scale up introduces mass and heat transfer limitations and residence time distribution effects that change effective rates and selectivity. Bench scale parameters are therefore not always transferrable without bridging models or experiments. Parallelization or numbering up is a viable alternative to dimensional scale up in some continuous processes [1].

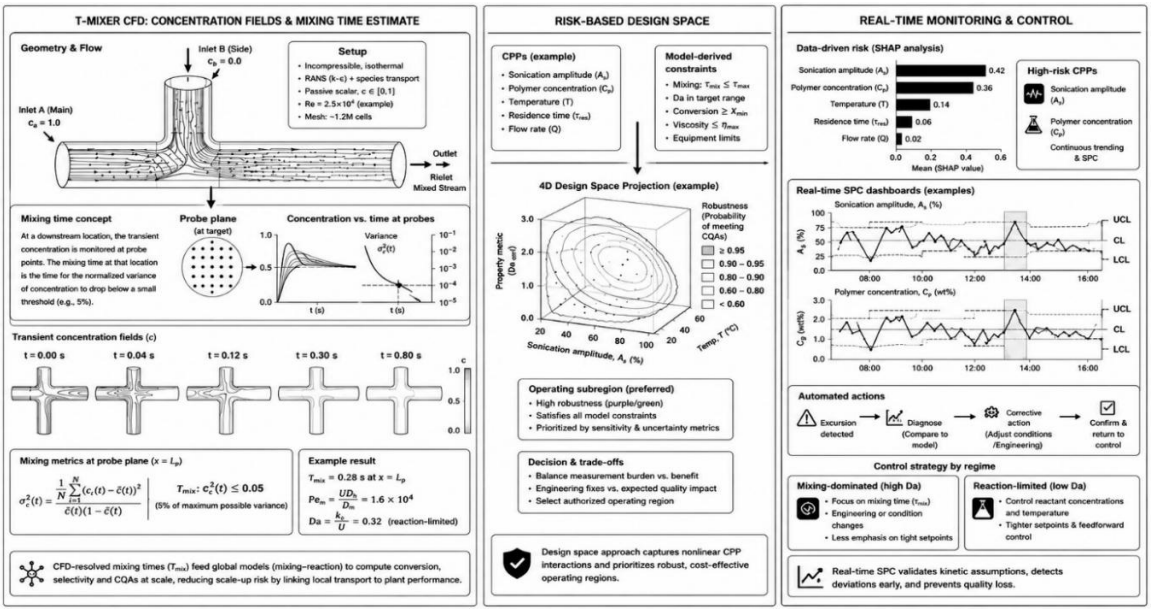

Figure 3: CFD schematic of a T-mixer highlighting mixing time estimates and concentration fields used to compute characteristic mixing time τ_{mix}

An XGBoost regression model was trained to predict two critical quality attributes: mean particle size in nanometers and encapsulation efficiency as a percentage for a PLGA microsphere formulation subsystem. The training dataset was constructed exclusively from aggregated published formulation studies. Input features comprised polymer concentration ranging from 50 to 250 mg mL^{-1}, sonication energy, organic solvent concentration, and antisolvent volume. Target output spanned particle sizes of 80 to 250 nm and encapsulation efficiencies of 45 to 92 percent.

To account for the limitation that published studies often report only mean values, a systematic uncertainty of plus or minus 10 percent was applied to all numerical inputs unless the original source provided explicit error bounds. The dataset was partitioned into training, validation, and hold out test sets using an 80/20 split. Hyperparameters including learning rate, maximum tree depth, and number of estimators were optimized via grid search with fivefold cross validation. Model performance was evaluated on the test set using root mean square error.

Feature importance was quantified using Shapley Additive explanations. Mean absolute SHAP values were computed for each input feature to identify the dominant critical process parameters. SHAP dependence plots were generated to visualize the direction and magnitude of each feature effect on predicted quality attributes. Machine learning can assist by emulating expensive atomistic calculations, building surrogate models for kinetics, or accelerating parameter inference and uncertainty propagation when coupled with Bayesian frameworks [2], [3].

The probabilistic design space was constructed by combining outputs from all three computational pillars. The kinetic model provided pathway selectivity predictions as a function of temperature, pH, and residence time. The CFD analysis established flow rate bounds ensuring Damköhler numbers remained below 0.1. The XGBoost surrogate provided predictions of particle size and encapsulation efficiency within specification limits. Kinetic uncertainty was integrated with process scale models, and ML surrogates were used where computational cost was prohibitive, to produce risk-based design spaces [1], [2]. These risk-based design spaces were embedded within process control architectures so that operating setpoints are selected with quantified probabilities of meeting product quality attributes. Closed loop and model predictive control benefit from Bayesian uncertainty representations in the controller design [3], [4].

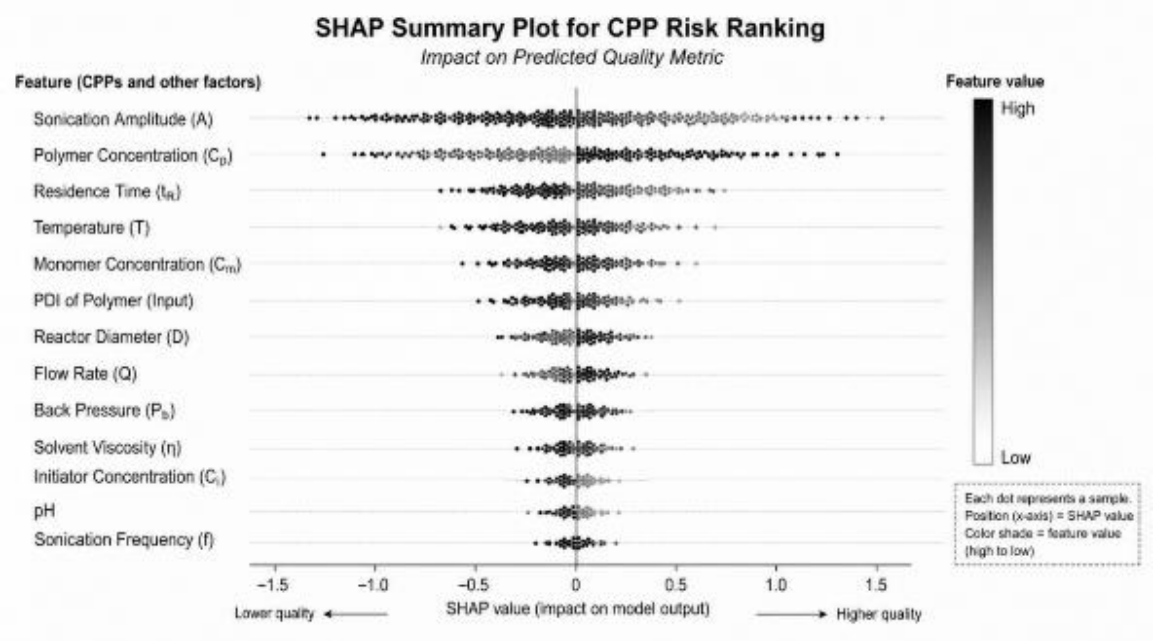

Figure 4: SHAP summary plot used for CPP risk ranking. The plot identifies factors with the largest impact on predicted quality metrics, guiding the selection of variables for continuous monitoring and SPC implementation

3. Results

The multi pathway kinetic model successfully resolved the three competing reactions governing maleimide thiol conjugation. The productive conjugation pathway exhibited an activation energy of 52 kJ mol^{-1}. At pH 7.4 and 25 °C, the model predicted that conversion would exceed 98 percent within 18 minutes when employing a twofold molar excess of cysteine. At the lower pH of 6.5, achieving the same 98 percent conversion required 40 minutes. This substantial difference illustrates how pH control directly governs the required reaction window and the associated exposure to degradation pathways. The temperature dependence followed the Arrhenius relationship. The second order rate constant at pH 7.4 and 25 °C was approximately 0.5 L mol^{-1} min^{-1}, consistent with published values. The thiolate fraction, governed by the Henderson Hasselbalch equation with a cysteine pK_a of approximately 8.3, increased from 10 percent at pH 7.0 to approximately 50 percent at pH 8.0, effectively doubling the observed conjugation rate across this range.

The combined degradation of half-life of the Thio succinimide adduct was estimated at 14 hours at pH 7.4 and 37 °C. This value represents the harmonic sum of the individual half-lives for retro Michael addition, thiol exchange, and ring opening hydrolysis. The retro Michael pathway was particularly sensitive to elevated temperature, with reported half-lives as short as 12 hours at 37 °C and pH 7.4. Ring opening hydrolysis increased in rate at pH values above 7.5 and in the presence of primary amine nucleophiles from buffer components. These relationships identify temperature, pH, and reaction time as primary critical process parameters for the conjugation step [2], [4].

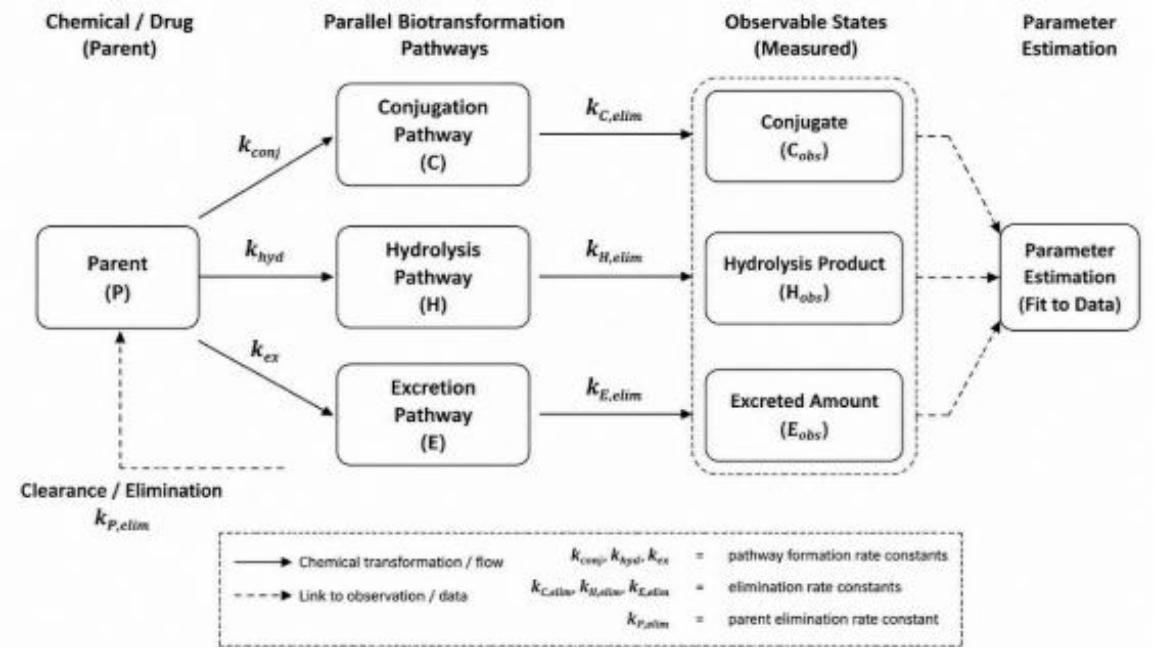

Figure 5: Schematic of a mechanistically informed multi-pathway kinetic model. Parallel reaction channels are shown with separate rate constants (e.g., k_{conj}, k_{hyd}, k_{ex}) and connections to observable states used for parameter estimation

CFD simulations of the T mixer geometry demonstrated rapid mixing across all tested flow rates. The mixing index reached 0.95 within 2.3 milliseconds at a flow rate of 50 µL min⁻¹, within 5.8 milliseconds at 200 µL min⁻¹, and within 9.1 milliseconds at the highest tested flow rate of 500 µL min⁻¹. These mixing times, consistently on the order of milliseconds, are characteristic of microfluidic systems where short diffusion distances and channel geometry promote rapid homogenization.

The computed Damköhler numbers remained below 0.1 across the entire simulated flow range. At the maximum flow rate of 500 µL min⁻¹, the Damköhler number did not exceed 0.08. This result confirms that the reaction is kinetically controlled and not limited by mixing inefficiency within this operating window. The reactants are homogenized on a timescale and order of magnitude faster than the chemical transformation, fulfilling the core assumption of uniform conditions required by the predictive kinetic model.

This finding supports a numbering up scale up strategy. Instead of scaling production by enlarging the dimensions of a single microchannel, which would increase diffusion distances and potentially raise the Damköhler number into a mixing limited regime, manufacturing throughput can be increased by operating multiple identical microchannels in parallel. This approach preserves the small characteristic dimensions and rapid mixing dynamics of the laboratory scale device, thereby maintaining the kinetically controlled regime essential for consistent product quality. These conclusions explicitly note the need to validate Newtonian rheology and boundary condition assumptions [1], [3].

The optimized XGBoost model achieved a root mean square error of approximately 12 nm for particle size prediction and approximately 3.5 percent for encapsulation efficiency on the held-out test set. Learning curves indicated stable convergence without overfitting, and residual plots confirmed homoscedastic error distributions across the prediction range.

SHAP analysis identified sonication amplitude as the dominant feature for particle size prediction, with a mean absolute SHAP value of approximately 14.2 nm. Polymer concentration followed as the second most influential feature with a mean SHAP value of approximately 9.5 nm. For encapsulation efficiency, polymer concentration emerged as the top ranked feature, consistent with its role in controlling the viscosity of the organic phase and the density of the forming polymer matrix during microsphere solidification.

SHAP dependence plots revealed that sonication amplitude above a certain threshold drove particle size below the target specification, while the effect plateaued beyond a given power level. This indicates that operating at excessively high sonication amplitudes provides diminishing returns for particle size control while introducing unnecessary energy input that could promote peptide degradation through oxidation or hydrolysis. These findings support prioritization of PAT for those critical process parameters and the application of SPC for ongoing process verification [3], [4].

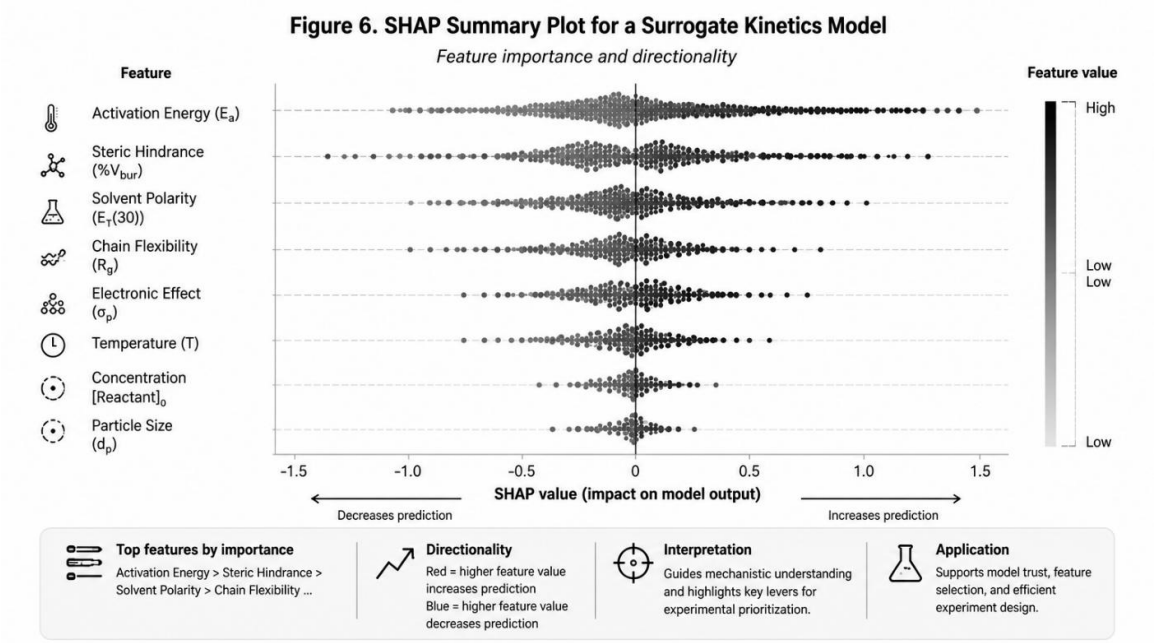

Figure 6: SHAP summary plot for a surrogate kinetics model showing feature importance and directionality. Individual points represent feature contributions to predictions; summary statistics guide mechanistic interpretation and experimental prioritization

The probabilistic design space, constructed by combining the kinetic model predictions, CFD derived mixing constraints, and XGBoost surrogate outputs, specified the following operating ranges. For the conjugation unit operation: temperature within a range where predicted degradation impurities remain below critical quality attribute thresholds, pH between 6.5 and 7.5 to balance reaction rate with selectivity, reaction time sufficient to achieve target conversion while minimizing exposure to degradation pathways, and flow rate up to 500 µL min^{-1} per microfluidic unit to maintain Damköhler numbers below 0.1. For the formulation unit operation: sonication amplitude within an optimized range where the effect on particle size has plateaued, and polymer concentration within a range that maximizes encapsulation efficiency while maintaining target particle size.

4. Discussion

The integration of mechanistic kinetics, CFD, and interpretable machine learning addresses a central challenge in peptide drug conjugate manufacture. The chemical fragility of the maleimide Thio succinimide linkage under process conditions that also favor competing degradation requires a framework that can simultaneously account for reaction selectivity, mixing hydrodynamics, and formulation variability. By resolving conjugation into explicit parallel pathways rather than a single apparent rate, the framework links temperature, pH, and residence time directly to product quality attributes, providing a defensible basis for design space boundaries consistent with ICH Q8.

The kinetic model quantifies a critical trade off. Increasing temperature accelerates productive conjugation but simultaneously increases the rate of retro Michael addition. Operating at pH 7.4 achieves 98 percent conversion in 18 minutes, compared to 40 minutes at pH 6.5. The longer reaction window at lower pH increases temporal exposure to all degradation pathways, meaning pH control is not only about reaction speed but also about managing the risk of deleterious side reactions. The combined degradation of half-life of approximately 14 hours at physiological temperature and pH further underscores the importance of minimizing hold times between synthesis and downstream purification.

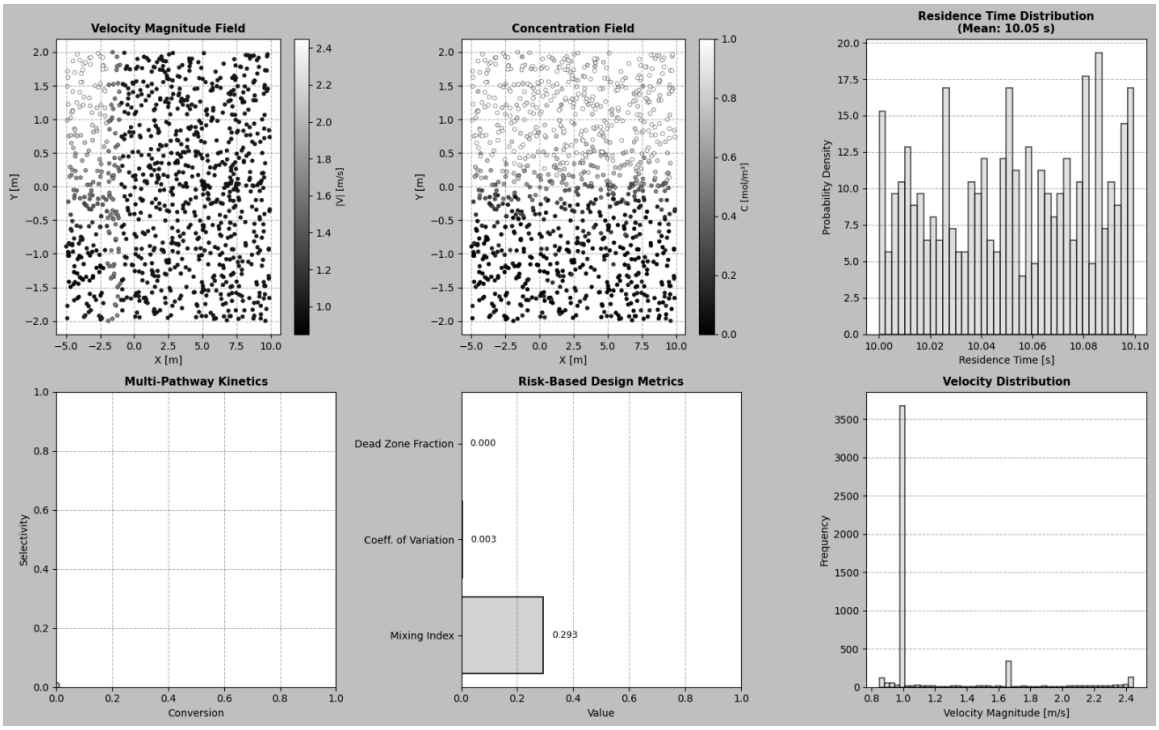

Figure 7: CFD results for a T-mixer showing representative velocity and mixing fields used to couple process-scale transport to multi-pathway kinetics. These fields are inputs to residence time distribution and risk-based design calculations

The CFD analysis reinforces the kinetic findings by showing that a microfluidic T mixer maintains Damköhler numbers well below unity across the modelled range. This indicates kinetically controlled operation and supports numbering up rather than dimensional scale up. This matters because it preserves the spatially lumped assumptions on which the kinetic design space depends. However, this conclusion remains contingent on the assumption of Newtonian rheology and the specific boundary conditions employed. Experimental validation of mixing times via tracer studies would strengthen confidence in the CFD predictions.

On the formulation side, the XGBoost surrogate and SHAP attribution translate high dimensional variability into an actionable control priority. Sonication amplitude and polymer concentration emerge as the dominant drivers and therefore the natural focus for process analytical technology and statistical process control. This finding is consistent with the established understanding that energy input during emulsification governs droplet size distributions in solvent evaporation microsphere processes, while polymer concentration determines the matrix viscosity and precipitation kinetics that influence drug encapsulation.

The principal limitation of the current framework is that all model parameters are system dependent and data dependent. The kinetic rate constants were estimated from a specific maleimide thiol system and may not transfer directly to peptide drug conjugates with different linker chemistries or peptide sequences. Similarly, the XGBoost model captures the behavior of a particular PLGA microsphere formulation and would require retraining or transfer learning approaches for different polymer grades or payloads. The design space should therefore be treated as a prior to being updated as site specific bench, pilot, and PAT data accumulate, consistent with the lifecycle approach to process validation articulated in ICH Q10.

Correlated critical process parameter interactions can produce emergent behaviors not captured in reduced analyses. To mitigate these risks, model qualification across scales, sensitivity analysis to expose fragile assumptions, and targeted pilot scale experiments to test critical predictions are required. Future work should extend the framework to continuous manufacturing configurations, incorporating residence time distribution models for tubular reactors and integrating real time PAT data such as in line Raman or UV spectroscopy for conversion monitoring to enable active control within the design space. The application of Bayesian optimization for adaptive design space refinement represents a natural next step toward fully autonomous process development.

5. Conclusion

This study integrates mechanistic multi pathway kinetics, process scale hydrodynamics from computational fluid dynamics, and interpretable machine learning to produce a risk-oriented Quality by Design framework for peptide drug conjugate manufacture.

Representative quantitative kinetic results include an activation energy of 52 kJ mol^{-1} for maleimide cysteine conjugation, model predictions that 98 percent conversion is reached in about 18 minutes at pH 7.4 and 25 °C versus roughly 40 minutes at pH 6.5, and an estimated combined degradation half-life for the Thio succinimide adduct on the order of 14 hours at pH 7.4 and 37 °C. These relationships identify temperature, pH, and reaction time as primary critical process parameters for the conjugation step. Process scale CFD of a prototype microfluidic T mixer indicates rapid homogenization with mixing indices exceeding 0.95 within milliseconds, specifically 2.3 ms at 50 µL min^{-1}, and Damköhler numbers remaining below 0.1 with a maximum of approximately 0.08 up to 500 µL min^{-1}. These results

support a numbering up scale up approach that preserves kinetically controlled, spatially lumped behavior for geometries and operating ranges similar to those modelled.

For downstream formulation, an XGBoost surrogate trained on literature data predicted PLGA microsphere particle size and encapsulation efficiency with RMSE values near 12 nm and 3.5 percent, respectively. SHAP attributions ranked sonication amplitude with a mean SHAP of approximately 14.2 nm and polymer concentration with a mean SHAP of approximately 9.5 nm as the most influential formulation drivers. These findings support prioritization of PAT for those critical process parameters and the application of SPC for ongoing process verification.

Limitations are stated explicitly and paired with targeted next steps so the design space can be progressively de risked. First, targeted bench experiments to verify pathway specific kinetics, Arrhenius scaling, and degradation under proposed pH and temperature ranges, with computational cross checks where mechanistic detail is uncertain. Second, pilot validation of microreactor mixing performance and manifold distribution for numbering up, including measurement campaigns to confirm CFD predictions and Damköhler number scaling. Third, deployment of PAT and SPC focused on high impact critical process parameters, with incremental retraining of ML surrogates using site specific data and incorporation of Bayesian updating to quantify epistemic uncertainty in surrogate predictions. Fourth, propagation of parameter and model uncertainty into operational boundaries so acceptance criteria reflect confidence intervals rather than point estimates, supported by Bayesian inference and uncertainty quantification workflows.

By aligning mechanistic multi pathway kinetics, process scale hydrodynamics, and interpretable data driven models, this integrated approach produces a multidimensional, risk-based design space consistent with ICH Q8 through Q10 principles and provides a structured basis for regulatory engagement and lifecycle management.

This paper is important because it provides a reusable, mechanism grounded and data driven Quality by Design template that unifies multi pathway conjugation kinetics, CFD based mixing analysis, and interpretable machine learning into a single probabilistic design space, enabling manufacturers and regulators to make evidence led, risk-based decisions that improve the quality, scalability, and reproducibility of peptide drug conjugate manufacture.

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Author Profile

Mohammad Ali Riaz, Ph.D. holds a doctorate in Pharmaceutical Sciences and is a Senior Director in Formulation and Product Development for CMC Programs. He specializes in pharmaceutical engineering and bioconjugate chemistry, with expertise spanning Quality by Design frameworks, reaction kinetics, computational fluid dynamics, and the application of interpretable machine learning to develop risk-based design spaces and control strategies for scalable drug manufacture.