RESEARCH PAPER

QUANTUM-DOT-ASSISTED ELECTRONIC SENSING AND MATHEMATICAL OPTIMIZATION OF pH-RESPONSIVE HYDROGEL DRUG DELIVERY: A COMPUTATIONAL FRAMEWORK

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ABSTRACT

Background: pH-responsive hydrogels are promising materials for controlled drug delivery because changes in environmental pH can influence polymer ionization, network swelling, and molecular transport. However, predicting drug-release behaviour and interpreting associated measurements remain challenging because of the coupled effects of polymer chemistry, drug diffusion, and measurement uncertainty. Mathematical modelling, quantum-dot-based optical transduction, and electronic signal processing provide complementary approaches for investigating these processes.

Objective: This study proposes an integrated computational framework combining pH-responsive hydrogel drug-release modelling, quantum-dot-assisted optical sensing, electronic signal processing, and mathematical optimization.

Methods: The framework is centred on a poly(2-hydroxyethyl methacrylate-co-methacrylic acid) (pHEMA-co-MA) hydrogel containing phenylpropanolamine as a reference drug. The proposed model connects pH-dependent hydrogel swelling with drug transport and release. A virtual quantum-dot optical module is introduced to represent a calibrated concentration-dependent measurement response, while an electronic signal-processing module is designed to examine the effects of sampling, measurement noise, baseline variation, and digital filtering. Numerical verification, comparison with published reference data, sensitivity analysis, uncertainty quantification, and multi-objective optimization are specified as evaluation procedures.

Results: The manuscript establishes the mathematical and computational structure required to investigate the coupled system. Quantitative performance, including drug-release prediction errors, numerical convergence, sensor-response characteristics, signal-processing metrics, and optimization outcomes, must be established through execution of the model and comparison with appropriate reference data. No unperformed simulations or experimental outcomes are presented as completed findings.

Conclusion: The proposed framework provides a structured computational approach for connecting pH-responsive hydrogel drug-release modelling with optical measurement and electronic signal interpretation. Its predictive accuracy and practical applicability remain to be established through reproducible numerical implementation, comparison with published experimental data, and independent validation of the proposed sensing mechanism.

Keywords: Controlled drug delivery; pH-responsive hydrogel; pHEMA-co-MA; phenylpropanolamine; quantum dots; fluorescence sensing; electronic signal processing; mathematical modelling; numerical simulation; multi-objective optimization.

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INTRODUCTION

1.1. Background of Controlled Drug Delivery Systems

The development of controlled drug delivery systems is an important area of pharmaceutical research because therapeutic effectiveness depends not only on the pharmacological activity of a drug but also on its release rate, absorption characteristics, and duration of exposure. Conventional drug administration may produce fluctuations in drug concentration, potentially resulting in periods of subtherapeutic exposure or concentrations exceeding the desired therapeutic range. Controlled-release formulations seek to regulate drug availability over a defined period and may reduce the frequency of administration required for certain therapeutic applications. The design of these systems therefore requires an understanding of

the interactions between drug properties, carrier composition, and the surrounding biological environment.

Polymeric hydrogels have attracted considerable attention as drug-delivery matrices because their three-dimensional networks can retain substantial quantities of water while providing pathways for molecular transport. Their structural and chemical properties can be modified through polymer selection, cross-linking density, functional-group composition, and network architecture. These characteristics influence drug loading, retention, and subsequent release. Hydrogels can also be designed to respond to environmental stimuli, including pH, temperature, and ionic strength, providing opportunities for controlled and site-dependent drug release.

Among stimuli-responsive systems, pH-sensitive hydrogels are particularly relevant to oral drug delivery because the gastrointestinal tract presents distinct pH environments. Polymers containing ionizable acidic or basic functional groups may undergo changes in ionization, electrostatic interactions, and network swelling as environmental pH changes. These responses can alter the diffusional pathways available to drug molecules and consequently influence release behaviour. The relationship between polymer ionization, swelling, and drug transport is therefore central to the design and mathematical description of pH-responsive delivery systems.

1.2. Chemical Mechanisms Governing Hydrogel Drug Release

Drug release from polymeric hydrogels may involve several mechanisms, including molecular diffusion, polymer relaxation, swelling, erosion, and degradation. The relative contribution of these mechanisms depends on the chemical composition of the polymer, the molecular characteristics of the drug, and the environmental conditions experienced by the formulation. In some systems, diffusion through the hydrated network may dominate release, whereas in others, polymer relaxation or structural changes may contribute substantially to the overall transport process.

The chemical characteristics of a hydrogel influence its interaction with both water and the incorporated drug. Ionizable functional groups may alter the local electrostatic environment, while polymer cross-linking can affect network dimensions and molecular mobility. Changes in swelling may modify the effective diffusion coefficient and the concentration gradient driving drug transport. Consequently, the release profile cannot always be described adequately by a single constant-rate assumption.

Mathematical representations are therefore useful for examining the relationships between formulation characteristics and release behaviour. Mechanistic transport models can provide insight into the influence of diffusion, boundary conditions, and material properties, while empirical kinetic equations offer practical descriptions of experimentally observed release profiles. However, the predictive value of any model depends on the assumptions made during its development and the availability of appropriate validation data.

1.3. Mathematical Modelling of Controlled Drug Release

Mathematical modelling provides a systematic means of investigating drug-release processes without requiring every possible formulation condition to be examined experimentally. The classical Higuchi model describes drug release from a matrix under specified assumptions and established an important foundation for the mathematical analysis of sustained-release systems. Subsequent empirical and semi-empirical approaches, including the Korsmeyer–Peppas model, have been used to characterize release profiles from polymeric systems and investigate the contribution of different transport mechanisms.

Although these models are valuable for interpreting release profiles, their application requires careful consideration of the assumptions underlying each equation. For example, a simplified diffusion model may not fully account for changes in hydrogel dimensions, time-dependent swelling, or concentration-dependent transport properties. In pH-responsive systems, the external environment may influence polymer ionization and swelling, introducing additional coupling between chemical conditions and drug transport.

Previous mathematical investigations of pH-responsive polymeric hydrogels have demonstrated the relevance of model-based analysis for examining the effects of formulation characteristics and environmental conditions. Similarly, coupled models incorporating ionic transport and hydrogel deformation have been developed to simulate swelling and drug-release kinetics, demonstrating the importance of accounting for interactions between transport and polymer-network behaviour.

These studies establish a foundation for computational investigation of hydrogel drug delivery. Nevertheless, the relationship between predicted drug concentration and the performance of an integrated monitoring system represents an additional dimension that can be examined through coupled modelling.

1.4. Quantum-Dot-Assisted Optical Sensing

Quantum dots are semiconductor nanocrystals whose optical properties are influenced by their composition, dimensions, and electronic energy structure. Their size-dependent optical behaviour is associated with quantum confinement, which can influence absorption and fluorescence emission characteristics. These properties have motivated research into quantum-dot-based optical sensing and biomedical applications.

Fluorescence-based sensing systems can provide a means of translating molecular interactions or environmental changes into measurable optical signals. Depending on the sensing mechanism, fluorescence response may be influenced by analyte concentration, surface functionalization, energy transfer, quenching, or changes in the local chemical environment. Quantum-dot-based hydrogel composites have also been investigated as sensing platforms, demonstrating the potential for combining polymeric matrices with fluorescent nanomaterials.[10]

For drug-delivery applications, however, the presence of a fluorescent material does not automatically establish a direct relationship between fluorescence intensity and drug concentration. Such a relationship requires a suitable recognition or transduction mechanism, an appropriate calibration function, and consideration of possible interference effects. Therefore, a computational sensing framework must distinguish between the optical response of a quantum dot and the analytical selectivity required for drug-specific measurement.

In the present study, quantum-dot-assisted sensing is considered as a virtual optical measurement module. Its purpose is to investigate how a specified concentration-dependent response, together with measurement uncertainty, could be integrated into a computational drug-release monitoring framework. The model is not interpreted as evidence of a fabricated or experimentally validated sensor.

1.5. Role of Electronics and Signal Processing in Drug-Release Monitoring

The practical interpretation of an optical sensing response requires an electronic measurement pathway capable of acquiring and processing the generated signal. In a fluorescence-based monitoring system, the optical response may be converted into an electronic signal through a suitable detector and acquisition circuit. The recorded signal can then be processed to reduce measurement noise, correct baseline variations, and estimate the corresponding concentration.

The quality of the measurement depends on several parameters, including detector sensitivity, sampling frequency, noise characteristics, baseline stability, and signal-processing procedures. In a computational investigation, these parameters can be varied systematically to examine their influence on signal quality and concentration-estimation accuracy.

Signal processing is particularly relevant when the measured response changes gradually over time, as may occur during controlled drug release. Excessive filtering may distort temporal features, whereas insufficient filtering may retain noise that affects concentration estimates. A virtual electronic acquisition model can therefore provide a framework for investigating these trade-offs before physical instrumentation is developed.

Integrating the electronic monitoring pathway with a mechanistic drug-release model may also permit investigation of uncertainty propagation. For example, uncertainty in the predicted concentration profile may influence the simulated optical response, while measurement noise may introduce additional uncertainty into the estimated release profile. Examining these relationships could provide useful information for the design of future experimental monitoring systems.

1.6. Research Gap and Rationale

Existing research has established the importance of mathematical modelling in hydrogel drug delivery, including models that incorporate pH-dependent swelling, diffusion, and polymer deformation.[7,8] Separately, quantum-dot-based hydrogel composites have been investigated for fluorescence sensing and related biomedical applications.[10] These research areas provide the scientific basis for developing an integrated computational approach.

However, the combined treatment of drug-release prediction, virtual quantum-dot optical response, electronic signal processing, and multi-objective formulation optimization requires further investigation within a clearly defined and reproducible framework. In particular, the influence of measurement uncertainty on the interpretation of predicted drug-release behaviour can be examined alongside the chemical and mathematical properties of the delivery system.

The present study therefore proposes a coupled computational framework in which a pH-responsive hydrogel model generates time-dependent drug concentrations, a virtual quantum-dot module represents the optical response, and an electronic signal-processing model evaluates measurement characteristics. Mathematical optimization is then intended to investigate the trade-offs between release behaviour and monitoring performance.

The proposed contribution is the integration and systematic computational evaluation of these components rather than the introduction of a new quantum-dot material or a claim of experimentally demonstrated drug detection. The originality of this integrated approach must be established through a focused comparison with existing literature and the results obtained from the implemented model.

1.7. Aim and Objectives

The principal aim of this study is to develop a reproducible computational framework integrating pH-responsive hydrogel drug-release modelling, quantum-dot-assisted optical sensing, electronic signal processing, and mathematical optimization.

The specific objectives are:

1. To formulate a mathematical model describing drug diffusion and pH-dependent swelling within a hydrogel matrix.

2. To investigate the influence of formulation parameters and environmental conditions on predicted cumulative drug release.
3. To develop a virtual quantum-dot fluorescence-response model for representing concentration-dependent optical measurements.
4. To simulate electronic signal acquisition and processing under different noise, sampling, and baseline conditions.
5. To evaluate numerical convergence, mass conservation, parameter sensitivity, and uncertainty propagation.
6. To develop a multi-objective optimization framework for examining the trade-offs between drug-release characteristics and sensing performance.
7. To establish a computational foundation for subsequent experimental validation of the proposed integrated system.

2. MATERIALS AND METHODS

2.1. Study Design and Computational Framework

The present study proposes an integrated computational framework for investigating pH-responsive hydrogel drug delivery combined with quantum-dot-assisted optical sensing, electronic signal processing, and mathematical optimization. The framework integrates chemical modelling, drug transport equations, optical response analysis, electronic signal acquisition, and numerical optimization within a unified computational environment.

The computational methodology is organized into five interconnected modules:

1. Hydrogel chemistry module: Describes pH-dependent ionization, polymer-network swelling, and the influence of environmental conditions on hydrogel structure.
2. Drug transport module: Simulates drug diffusion and release through the hydrated polymer network using mathematical transport equations.
3. Quantum-dot sensing module: Represents the optical response of quantum dots as a function of analyte concentration and relevant environmental conditions.
4. Electronic signal-processing module: Models signal acquisition, measurement noise, digital filtering, and conversion of optical measurements into concentration estimates.
5. Mathematical optimization module: Evaluates the trade-offs between drug-release performance, sensing accuracy, and robustness under parameter uncertainty.

The modules are coupled through the time-dependent drug concentration, hydrogel swelling state, environmental pH, and optical response. The computational workflow is designed to investigate the feasibility of combining controlled drug release with a modelled sensing system.

The study is computational in nature and does not assume experimental confirmation of the proposed integrated system. The established hydrogel–drug model provides the basis for the drug-release component, while the sensing and optimization components constitute the proposed computational extension.

2.2. Selection of the Reference Hydrogel–Drug System

The computational investigation is based on a pH-responsive copolymer hydrogel composed of poly(2-hydroxyethyl methacrylate-co-methacrylic acid) (pHEMA-co-MA), with phenylpropanolamine (PPA) selected as the reference drug molecule. This system has previously been examined through mathematical modelling of hydrogel swelling and drug-release behaviour.

The methacrylic acid component contains ionizable carboxylic acid groups that respond to changes in environmental pH. Changes in ionization influence electrostatic interactions within the polymer network and consequently affect its swelling behaviour. The resulting changes in network hydration and structure influence the effective diffusivity of the drug and its release kinetics.

Phenylpropanolamine is selected because its release from pHEMA-co-MA hydrogels has been considered in a previously published mathematical investigation. This provides a literature-supported basis for examining the relationship between hydrogel deformation, transport processes, and drug release.

The present study does not claim to reproduce the original model as a new contribution. Instead, the established hydrogel–drug system serves as the reference for developing an extended computational framework incorporating optical sensing, electronic signal processing, uncertainty analysis, and multiobjective optimization.

The investigation distinguishes three levels of modelling:

- Established hydrogel swelling and drug-transport mechanisms.
- Proposed computational extension involving optical sensing and electronic signal processing.
- Integrated mathematical evaluation of release performance, sensing accuracy, and system-level trade-offs.

The optical sensing component is treated as a separate transduction model until a specific quantum-dot formulation and a validated drug-recognition mechanism are established. Therefore, the framework does not assume that fluorescence intensity is inherently a direct measure of phenylpropanolamine concentration.

2.3. pH-Dependent Ionization and Hydrogel

Swelling

The pH-responsive behaviour of pHEMA-co-MA is associated with the ionization of methacrylic acid groups within the polymer network. The degree of ionization can be represented using an acid–base equilibrium relationship:

$$\alpha = \frac{1}{1 + 10^{(pK_a - pH)}}$$

where α is the fraction of ionized carboxylic acid groups, pK_a is the apparent acid dissociation constant of the polymer, and pH represents the surrounding medium.

This expression provides a simplified representation of pH-dependent ionization. The apparent pK_a of a polymer network may differ from that of the corresponding free monomer because of electrostatic interactions and local environmental effects. Accordingly, the value used in the computational model must be obtained from an appropriate literature source or justified parameter-estimation procedure.

The equilibrium swelling ratio may be expressed as:

$$Q = \frac{V_{\text{swollen}}}{V_{\text{dry}}}$$

where$Q$ is the volumetric swelling ratio, V_{swollen} is the hydrated polymer volume, and V_{dry} is the dry polymer volume.

A general constitutive relationship may be used to represent the dependence of swelling on pH and polymer composition:

$$Q_{\text{eq}} = f(pH, \alpha, \phi_p, \nu_e, T)$$

where Q_{eq} is the equilibrium swelling ratio, $\phi_p$is the polymer volume fraction, $\nu_e$represents the effective crosslink density, and T is temperature.

The specific form of the swelling function must be selected according to the available experimental or literature data. The relationship should not be treated as a universal constitutive law without parameter identification and validation.

2.4. Dynamic Swelling Kinetics

The time-dependent swelling response is represented using a relaxation-based formulation:

$$\frac{dQ}{dt} = \frac{Q_{\text{eq}} - Q(t)}{\tau_s}$$

where$Q(t)$ is the instantaneous swelling ratio, Q_{eq} is the equilibrium swelling ratio under the prevailing conditions, and τ_s is the characteristic swelling-relaxation time.

This equation provides a simplified means of representing the approach toward equilibrium swelling. It may be used for preliminary computational analysis when a more detailed polymer-relaxation model is not available.

The swelling-relaxation time should be determined from published swelling data or parameter estimation. If the environmental pH changes during the simulation, the equilibrium swelling ratio must be updated according to the new conditions.

The simplified relaxation equation is not intended to replace more detailed models of solvent transport and polymer-chain relaxation. Its suitability must be assessed by comparing its predictions with the available swelling data.

2.5. Drug Diffusion and Transport Model

Drug transport within the hydrogel is described using a diffusion-based mass-conservation equation:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D_{\text{eff}} \nabla C)$$

where$C$ is the drug concentration within the hydrogel, t is time, and $D_{\text{eff}}$is the effective drug diffusivity.

For a one-dimensional planar hydrogel with spatial coordinate x, the equation becomes:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D_{\text{eff}} \frac{\partial C}{\partial x}\right)$$

The effective diffusivity is treated as a function of hydrogel hydration:

$$D_{\text{eff}} = D_{\text{eff}}(Q)$$

A free-volume-based relationship may be considered to represent the influence of hydration on molecular mobility. The precise functional form and its parameters must be selected from the reference model or identified using appropriate data.

The governing equation is intended to represent drug diffusion within a dynamically changing polymer network. Where swelling produces substantial geometric deformation, the model must account for the changing domain or use an appropriate coordinate transformation. A fixed-domain approximation should only be adopted when its assumptions are justified.

2.6. Initial and Boundary Conditions

The initial drug concentration within the hydrogel is represented as:

$$C(x, 0) = C_0(x)$$

where \(C_0(x)\) is the initial spatial distribution of drug concentration.

For a uniformly loaded hydrogel, the initial condition may be simplified to:

$$C(x, 0) = C_0$$

The boundary conditions depend on the geometry and release-medium configuration. For a symmetric hydrogel, a zero-flux condition may be applied at the centre plane:

$$\left.\frac{\partial C}{\partial x}\right|_{x=0} = 0$$

At the hydrogel–medium interface, the outward drug flux may be represented using a mass-transfer boundary condition:

$$J = k_m(C_s - C_b)$$

where J is the outward drug flux, k_m is the external mass-transfer coefficient, $C_s$is the drug concentration at the hydrogel surface, and C_b is the bulk concentration in the release medium.

Under ideal sink conditions, the bulk concentration is assumed to remain sufficiently low relative to the interfacial concentration. In this case, the boundary condition may be simplified accordingly.

The initial and boundary conditions must be selected

consistently with the geometry and experimental conditions of the reference dataset used for validation.

2.7. Finite-Volume Release-Medium Model

When sink conditions cannot be assumed, the concentration of drug in the surrounding medium is calculated using a finite-volume mass balance:

$$V_m \frac{dC_b}{dt} = AJ$$

where V_m is the volume of the release medium, $C_b$is the bulk drug concentration, A is the exposed hydrogel surface area, and J is the outward flux from the hydrogel.

For a medium undergoing replacement or continuous flow, the balance may be extended as:

$$V_m \frac{dC_b}{dt} = AJ - Q_f C_b$$

where Q_f is the volumetric flow rate of the release medium. This expression assumes that the incoming medium contains negligible drug and that the outflow concentration equals the well-mixed bulk concentration.

The finite-volume model is relevant when the external concentration is expected to influence the concentration gradient across the hydrogel interface. Sink and finite-volume cases are treated as separate computational scenarios rather than combined into a single assumption.

2.8. Quantum-Dot Optical Sensing Model

The optical sensing module represents the fluorescence response of quantum dots as a function of analyte concentration and environmental conditions. Quantum dots are considered because their optical properties can be influenced by their size, surface chemistry, surrounding medium, and interactions with nearby molecules.

The measured fluorescence intensity is represented by:

$$I(t) = I_0 + g(C_a(t), pH, T) + \epsilon(t)$$

where $I(t)$ is the measured fluorescence intensity, I_0 is the baseline intensity, g is the analyte-dependent optical response, $C_a(t)$ is the analyte concentration, pH is the environmental pH, T is temperature, and$\epsilon(t)$ represents measurement noise.

For an initial calibration model, a linear response may be assumed over a restricted concentration range:

$$I = I_0 + k_s C_a + \epsilon$$

where$k_s$is the optical sensitivity coefficient.

If the optical response exhibits saturation, a nonlinear calibration function may be considered:

$$I = I_0 + \frac{I_{\max} C_a}{K_s + C_a} + \epsilon$$

where$I_{\max}$is the maximum analyte-dependent fluorescence contribution and $K_s$is a characteristic concentration parameter.

The appropriate calibration function must be selected based on the sensing mechanism and supporting data. These equations represent alternative model forms and are not assumed to describe the same sensor simultaneously.

A critical distinction is maintained between drug release and drug sensing. The analyte concentration used in the optical model must correspond to a chemically justified recognition mechanism. If the quantum dots respond to pH rather than directly to the drug, the sensor output should be interpreted as an environmental measurement, not as a direct measurement of drug concentration.

2.9. Electronic Signal Acquisition and Processing

The electronic module converts the simulated optical response into a digital signal suitable for computational analysis. The continuous optical signal is sampled at a specified sampling interval:

$$t_n = n\Delta t_s$$

where t_n is the n-th sampling time, Δt_s is the sampling interval, and n is the sample index.

The sampled signal is expressed as:

$$I_n = I(t_n) + \eta_n$$

where $\eta_n$represents electronic and measurement noise.

For an initial simulation, additive Gaussian noise may be considered:

$$\eta_n \sim \mathcal{N}(0, \sigma_n^2)$$

where σ_n is the standard deviation of the noise distribution.

The signal-to-noise ratio is calculated as:

$$SNR = 10 \log_{10}\left(\frac{P_s}{P_n}\right)$$

whereP_s and $P_n$denote signal power and noise power, respectively.

A moving-average filter may be used as a baseline signal-processing method:

$$\bar{I}_n = \frac{1}{M}\sum_{j=0}^{M-1} I_{n-j}$$

where $\bar{I}_n$is the filtered signal and M is the filter-window length.

The filtered signal is subsequently converted into an estimated analyte concentration using the inverse calibration function:

$$\hat{C}_a = f^{-1}(\bar{I})$$

where f^{-1} represents the inverse of the selected calibration model.

The sensing error is evaluated using the root mean square error:

$$RMSE_C = \sqrt{\frac{1}{N}\sum_{n=1}^{N}\left(\hat{C}_{a,n} - C_{a,n}\right)^2}$$

where N is the number of samples, $\hat{C}_{a,n}$ is the estimated concentration, and$C_{a,n}$ is the reference concentration supplied to the simulated sensing system.

The signal-processing analysis will compare unfiltered and filtered signals to quantify the influence of noise reduction on concentration-estimation accuracy. This module represents the ECE contribution through signal acquisition, digital

filtering, and measurement-system performance analysis.

2.10. Coupling of the Hydrogel, Drug-Release, and Sensing Modules

The modules are connected through a sequential computational procedure.

First, the environmental pH is supplied to the hydrogel chemistry model. The degree of ionization and swelling state are calculated using the selected constitutive relationships. The resulting swelling ratio is used to update the effective drug diffusivity.

Second, the drug transport equation is solved to obtain the spatial concentration distribution and the outward drug flux. The flux is integrated to determine the cumulative released amount.

Third, the drug concentration or a chemically justified proxy-analyte concentration is supplied to the optical sensing model. The corresponding fluorescence intensity is calculated and sampled at the prescribed electronic acquisition frequency.

Fourth, the sampled signal is processed to estimate the analyte concentration. The estimated concentration is compared with the reference concentration to determine sensing error.

Finally, the release and sensing performance indicators are passed to the optimization module.

This coupling strategy enables the evaluation of the interaction between chemical response, drug transport, optical transduction, and electronic measurement without assuming that the individual modules have already been experimentally integrated.

2.11. Numerical Implementation and Convergence Assessment

The governing transport equation will be discretized using a spatial finite-difference or finite-volume method. Time integration will be performed using an appropriate numerical scheme selected according to the stability and accuracy requirements of the coupled equations.

The numerical solution will be assessed through a systematic refinement study. Simulations will be repeated using progressively finer spatial and temporal discretizations, and the resulting release profiles will be compared.

The relative difference between two successive numerical solutions may be calculated as:

$$E_{\text{ref}} = \frac{\left\| R_h - R_{h/2} \right\|_2}{\left\| R_{h/2} \right\|_2}$$

where R_h is the release profile obtained using the coarser discretization, $R_{h/2}$ is the release profile obtained using the refined discretization, and $\|\cdot\|_2$ denotes the Euclidean norm.

The numerical solution will be considered sufficiently refined when further discretization changes produce differences below a predefined tolerance. The tolerance must be specified before the final simulations and reported in the completed manuscript.

Mass conservation will be checked by comparing the initial drug loading with the sum of the drug remaining in the hydrogel and the cumulative amount released into the medium. Any discrepancy will be reported as a numerical mass-balance error.

2.12. Model Verification and Validation Strategy

Model verification and model validation will be treated as separate procedures.

Verification will examine whether the numerical implementation correctly solves the selected mathematical equations. It will include:

- Grid-refinement assessment.
- Time-step refinement.
- Mass-balance evaluation.
- Comparison with analytical solutions for simplified limiting cases.
- Reproducibility checks using identical initial conditions and parameters.

Validation will assess whether the mathematical model adequately represents the behaviour of a real hydrogel–drug system. This will require comparison with independently published experimental datasets or new measurements.

Where suitable published data are available, simulated cumulative release profiles will be compared with the corresponding experimental observations using statistical measures such as RMSE and the coefficient of determination. The source dataset, experimental conditions, and parameter-estimation procedure must be clearly reported.

If no appropriate independent dataset is available, the study will be described as a computational framework with numerical verification rather than as an experimentally validated predictive model. This distinction is essential to avoid overstating the evidential strength of the proposed method.

2.13. Sensitivity and Uncertainty Analysis

Sensitivity analysis will be performed to identify the parameters that exert the greatest influence on drug release and sensing performance.

The parameters considered may include polymer ionization constant, equilibrium swelling parameters, reference drug diffusivity, swelling-dependent diffusivity coefficient, hydrogel thickness, external mass-transfer coefficient, optical sensitivity, baseline fluorescence intensity, electronic noise variance, sampling interval, and filter-window length.

A normalized local sensitivity coefficient may be calculated as:

$$S_{y,p} = \frac{p}{y}\frac{\partial y}{\partial p}$$

where y is the selected model output and p is the parameter under investigation.

The sensitivity analysis will examine the influence of each parameter on cumulative drug release, release duration, concentration-estimation error, and signal-to-noise ratio.

Uncertainty analysis will be conducted by assigning

probability distributions to parameters for which uncertainty estimates are available. Monte Carlo sampling may then be used to propagate parameter uncertainty through the coupled model.

The resulting output distributions will be summarized using suitable descriptive statistics and confidence or credible intervals, depending on the adopted statistical framework. Parameter distributions must be justified by literature evidence or explicitly identified as exploratory assumptions.

2.14. Multiobjective Mathematical Optimization

The optimization module is designed to identify parameter combinations that balance drug-release performance and sensing accuracy.

The optimization problem will consider three principal objectives.

Objective 1: Minimize undesirable initial burst release

$$\min_{\mathbf{x}} f_1(\mathbf{x}) = F(t_b; \mathbf{x})$$

where t_b is a predefined early-release time, F is the cumulative fraction of drug released, and $\mathbf{x}$ represents the vector of design parameters.

Objective 2: Minimize sensing error

$$\min_{\mathbf{x}} f_2(\mathbf{x}) = RMSE_C(\mathbf{x})$$

where $RMSE_C$ represents the concentration-estimation error obtained from the electronic sensing module.

Objective 3: Improve delivery performance

A target-based objective may be defined as:

$$\min_{\mathbf{x}} f_3(\mathbf{x}) = |F(t^*; \mathbf{x}) - F^*|$$

where t^* is the selected evaluation time and F^* is the desired cumulative release fraction.

The optimization problem is subject to physically meaningful constraints, including positive diffusivity, bounded swelling ratios, permissible hydrogel dimensions, and valid optical calibration ranges.

A multiobjective evolutionary algorithm or another suitable numerical optimizer may be employed to identify a Pareto-optimal set of solutions. The resulting Pareto front will illustrate the trade-offs between early burst release, target delivery, and sensing error.

The optimization results will not be interpreted as a universally optimal formulation. Instead, they will represent parameter combinations that are optimal within the specified mathematical model, parameter bounds, and objective definitions**.**

2.15. Computational Software and Reproducibility

The computational framework may be implemented using Python, MATLAB, or an equivalent numerical computing environment. The selected software version, numerical libraries, solver settings, optimization algorithm, random seeds, and parameter files must be documented in the final manuscript.

To support reproducibility, the completed study should provide:

- Governing equations and parameter definitions.
- Parameter values and their sources.
- Initial and boundary conditions.
- Numerical discretization settings.
- Optimization constraints and stopping criteria.
- Scripts used to generate figures and tables.
- Data files used for verification and validation.
- Random seeds for stochastic simulations.

The computational code and supporting data should be made available through an appropriate repository when permitted by the journal and applicable data-use conditions.

Table 3. Model parameters, definitions, and data requirements

Parameter	Description	Unit or representation	Required source
pK_a	Apparent acid dissociation constant of polymer	Dimensionless	Published material data or estimation
Q	Hydrogel swelling ratio	Dimensionless	Swelling data
D	Effective drug diffusivity	cm²/s	Reference transport data
L	Hydrogel half-thickness	cm	Experimental geometry
C_0	Initial drug concentration	Concentration/volume	Loading conditions
k_m	External mass-transfer coefficient	Consistent with flux formulation	Experimental conditions or estimation
I_0	Baseline fluorescence intensity	Instrument-dependent	Optical calibration
S	Optical sensitivity coefficient	Intensity/concentration	Calibration data
σ	Measurement-noise standard deviation	Same unit as signal	Measurement characterization
Δt	Sampling interval	s	Acquisition configuration

N	Filter-window length	Samples	Signal-processing configuration

Note: This table identifies the parameters required by the proposed framework. Numerical values should be entered only after their sources and units have been verified.

2.16. Ethical Considerations

The proposed study is computational in nature and does not involve human participants, animal experiments, or the collection of identifiable personal data. Therefore, institutional ethical approval is not anticipated to be required for the computational work itself. Any future experimental extension involving biological materials, animals, or human participants would require the relevant institutional approvals before commencement.

3. RESULTS AND DISCUSSION

3.1. Preliminary evaluation of drug-release models

The preliminary computational investigation examined the release behaviour of phenylpropanolamine (PPA) from a pH-responsive hydrogel using constant-diffusion, Weibull, and hydration-dependent diffusion models. The objective was to investigate whether incorporating hydration-associated changes in drug diffusivity could improve the description of cumulative drug release.

The constant-diffusion model provided a baseline representation of drug transport, whereas the Weibull model described the release profile through an empirical kinetic relationship. The hydration-dependent model incorporated changes in effective diffusivity associated with hydrogel hydration, thereby providing a mathematical representation of the interaction between polymer swelling and molecular transport.

The preliminary model comparisons indicated that the predicted release profiles were sensitive to the selected kinetic representation. These findings support further investigation of hydration-dependent transport, although the models require evaluation using verified experimental data before their predictive performance can be established.

3.2. Comparison of constant-diffusion and hydration-dependent models

Table 1. Preliminary model-performance comparison using the current approximate dataset.

Performance metric	Constant diffusion	Hydration-dependent diffusion
RMSE	0.04034	0.02768
MAE	0.03565	0.020529
R^2	0.91253	0.99153
AIC	−68.637857	−73.407162
BIC	−68.239962	−72.213476

The hydration-dependent model produced lower RMSE and MAE values than the constant-diffusion model. Its higher coefficient of determination also indicates closer agreement with the approximate observations used in this analysis. The lower AIC and BIC values provide additional support for the hydration-dependent model under the assumptions and fitting procedure adopted.

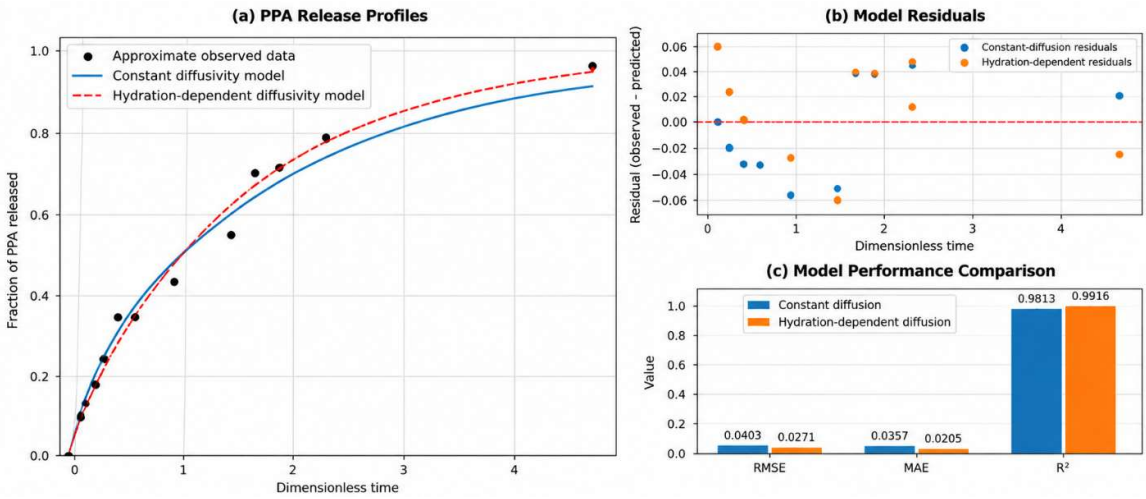


Figure 1. Comparison of constant-diffusivity and hydration-dependent diffusivity models for predicting cumulative phenylpropanolamine (PPA) release from a pH-responsive hydrogel. (a) Predicted release profiles and approximate observed data, (b) residual distributions, and (c) model-fitting performance metrics.

These results suggest that incorporating hydration-associated changes in diffusivity may improve the representation of PPA release kinetics. However, the observed differences should be interpreted as preliminary model-comparison outcomes rather than definitive evidence of improved predictive accuracy. Independent validation and consistent parameter estimation are required to establish whether the improvement persists across experimental conditions.

3.3. Influence of hydration on drug diffusivity

The computational analysis also examined the relationship between hydrogel hydration and the effective diffusivity of PPA. The simulated hydration profile increased over dimensionless time, while the corresponding diffusivity increased from approximately 5.387×10^{-8} to 4.826×10^{-7} cm^2/s.

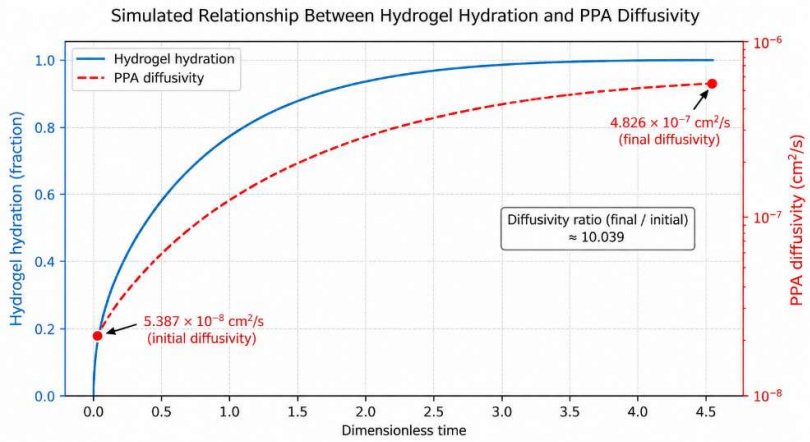


Figure 2. Simulated relationship between hydrogel hydration and PPA diffusivity. The plotted curve represents the current model implementation and should be checked against the original parameterization before publication.

The increase in effective diffusivity is consistent with the model assumption that hydration modifies the transport environment within the polymer network. As the hydrogel absorbs water, changes in network structure and available free volume may influence the mobility of incorporated drug molecules.

The simulated diffusivity ratio was approximately 10.039 between the reported initial and final states. This ratio is a model-derived quantity and should not be interpreted as a universally applicable material property. Its physical relevance depends on the adopted hydration–diffusivity relationship and the experimental conditions used to parameterize it.

3.4. Comparison of characteristic release times

The characteristic times required to reach selected

cumulative-release targets were compared between the constant-diffusion and hydration-dependent models.

Table 2. Preliminary characteristic release times expressed in dimensionless time units.

Target release	Constant diffusion	Hydration-dependent diffusion	Reduction
50%	0.1968	0.1677	14.8%
90%	0.8410	0.5343	37.0%
95%	1.1290	0.6531	42.2%

The preliminary simulations indicate that the hydration-dependent model reaches the selected release targets at shorter dimensionless times. The difference between the models becomes more pronounced at higher release fractions, suggesting that the assumed hydration-dependent diffusivity has a greater influence on the later stages of the simulated release process.

This behaviour highlights the importance of considering time-varying transport properties when modelling responsive hydrogel systems. Nevertheless, the characteristic times are specific to the current dimensionless formulation and cannot be converted into physical release times without a verified time-scale definition.

3.5. Model residuals and goodness of fit

Residual analysis was performed to examine the differences between the observed and predicted release fractions. The residuals were calculated as:

$$e_i = F_{\text{observed},i} - F_{\text{predicted},i}$$

The preliminary residual plots showed deviations on both sides of the zero-residual line. This indicates that neither model reproduced every approximate observation exactly. Some systematic variation was visible across the sampled dimensionless time range, particularly around intermediate release fractions.

The residual patterns suggest that additional evaluation is needed to determine whether the remaining differences arise from model assumptions, approximate digitization, parameter estimation, or the underlying variability of the reference measurements. Residual analysis should therefore be repeated using the verified dataset before final conclusions are drawn.

3.6. Virtual Quantum-Dot Optical Response

The quantum-dot optical module was formulated as a virtual measurement component to investigate the potential integration of fluorescence-based sensing with hydrogel drug-release modelling. The module represents the relationship between analyte concentration and fluorescence intensity through a mathematical calibration function. This approach enables the influence of optical sensitivity, baseline variation, and measurement noise to be examined within the computational framework.

The simulated optical response is conceptually linked to the concentration profile generated by the drug-transport model. However, the relationship between fluorescence intensity and phenylpropanolamine concentration depends on the availability of a chemically appropriate recognition or transduction mechanism. In the absence of an experimentally established quantum-dot formulation and calibration dataset, the simulated response should be interpreted as a hypothetical measurement model rather than evidence of direct drug detection.

The virtual sensing module provides a basis for evaluating how uncertainty in optical measurements may influence the interpretation of predicted drug-release behaviour. Further work involving material selection, surface functionalization, calibration experiments, and interference testing will be required to establish the analytical performance of a practical sensing system.

3.7. Electronic Signal Processing and Measurement Considerations

The electronic signal-processing component is intended to examine the effects of sampling, measurement noise, baseline variation, and digital filtering on the interpretation of the simulated optical response. These factors are relevant to the development of a reliable measurement pathway because the quality of the acquired signal may influence the accuracy of concentration estimation.

The computational framework incorporates signal acquisition and filtering as sequential operations. The sampled optical response is considered the input to the electronic processing module, while the filtered signal provides the basis for estimating the corresponding analyte concentration. The difference between the reference concentration and the estimated concentration can subsequently be used to evaluate measurement error.

The selection of sampling frequency and filter-window length involves a potential trade-off between noise reduction and preservation of temporal information. Although filtering may reduce random fluctuations, excessive smoothing may distort changes in the signal associated with the underlying release process. Therefore, the electronic module should be evaluated using consistent input signals and predefined performance measures.

The present framework establishes the mathematical structure for this evaluation. Quantitative conclusions regarding signal-to-noise ratio, filtering efficiency, and concentration-estimation accuracy require execution of the corresponding simulations and verification against the selected reference signal.

3.8. Sensitivity and Uncertainty Considerations

The predicted behaviour of the integrated hydrogel–drug delivery system may depend on several parameters, including polymer ionization characteristics, equilibrium swelling, effective drug diffusivity, hydrogel dimensions, and external mass-transfer conditions. The virtual optical and electronic modules introduce additional sources of uncertainty associated with calibration sensitivity, baseline fluorescence, measurement noise, sampling interval, and filtering settings.

Sensitivity analysis provides a systematic means of identifying parameters that exert a substantial influence on model outputs. Within the proposed framework, relevant outputs include cumulative drug release, characteristic release time, concentration-estimation error, and signal-to-noise ratio. The resulting sensitivity information may help identify parameters requiring more precise experimental characterization.

Uncertainty propagation is also important because uncertainties in material properties and measurement conditions may affect the interpretation of the predicted release profile. Monte Carlo sampling can be used to investigate the resulting distributions of model outputs when suitable parameter distributions are available.

At the present stage, these analyses are specified as components of the computational methodology. Their quantitative outcomes should be reported only after the simulations have been completed using justified parameter ranges and reproducible computational procedures.

3.9. Multiobjective Optimization Framework

The proposed optimization framework is intended to investigate the trade-offs between drug-release characteristics and measurement performance. The formulation of the optimization problem considers early burst release, achievement of a target cumulative-release fraction, and concentration-estimation error as relevant performance objectives. These objectives may compete with one another. For example, a parameter combination that modifies the release rate may also influence the time-dependent concentration profile supplied to the virtual optical measurement module. Consequently, optimization of release behaviour alone may not represent the complete performance of an integrated delivery and monitoring system.

A multiobjective evolutionary algorithm or another suitable numerical optimization method may be employed to identify parameter combinations that satisfy the specified constraints. The resulting Pareto-optimal solutions would represent alternative trade-offs within the mathematical model rather than a single universally optimal formulation.

The practical interpretation of the optimization outcomes depends on the validity of the underlying transport model, the reliability of the optical calibration function, and the suitability of the selected parameter bounds. Accordingly, the proposed optimization framework should be regarded as a computational design approach until its predictions have been assessed using verified data and, where appropriate, experimental measurements.

4. CONCLUSION AND FUTURE PERSPECTIVES

This study presents a computational framework for connecting pH-responsive hydrogel drug-release modelling with quantum-dot-assisted optical measurement, electronic signal processing, and mathematical optimization. The framework is centred on a pHEMA-co-MA hydrogel containing phenylpropanolamine as a reference drug system and considers the influence of hydrogel hydration on effective drug diffusivity.

The preliminary model comparison illustrates the potential importance of representing hydration-associated changes in diffusivity when describing drug-release behaviour. However, the numerical outcomes remain dependent on the accuracy of the approximate input dataset, the selected model assumptions, and the parameter-estimation procedure. Independent validation using suitable experimental data is therefore necessary before predictive performance can be established.

The proposed optical and electronic modules extend the framework beyond conventional drug-release modelling by providing a mathematical structure for examining concentration-dependent measurement responses, signal acquisition, noise, and filtering. Nevertheless, the present computational formulation does not demonstrate a fabricated quantum-dot sensor or establish direct analytical detection of phenylpropanolamine. A chemically justified recognition mechanism and experimental calibration are required to support such an application.

Future work should prioritize verification of the numerical implementation, refinement of the hydrogel transport model, and validation against independently sourced experimental release data. Further investigation should also establish an appropriate quantum-dot material and recognition mechanism, characterize the optical response under relevant environmental conditions, and evaluate the performance of the electronic acquisition and processing pathway. Once these components are supported by reliable data, sensitivity analysis, uncertainty quantification, and multiobjective optimization can be used to examine the design trade-offs of the integrated system.

Overall, the proposed framework provides a structured computational basis for investigating the relationship between responsive hydrogel chemistry, drug transport, optical measurement, and electronic signal interpretation. Its predictive reliability and practical applicability remain to be established through reproducible implementation and systematic validation

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