

Controlled Drug Release from Biodegradable Implants

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ABSTRACT

Biodegradable implants fabricated from poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(ortho esters), and silk fibroin offer programmable drug release lasting weeks to years while eliminating the need for surgical retrieval, yet achieving predictable, reproducible release kinetics from degrading polymer matrices remains a persistent formulation challenge. The interplay between polymer chain scission, crystallinity evolution, pore formation, osmotic pressure, and local pH changes creates complex, non-linear release profiles that deviate substantially from theoretical predictions based on simple diffusion or erosion models. This study presents the Biodegradable Implant Drug Release Assessment Framework (BIDRAF), evaluating five controlled release strategies -- monolithic PLGA matrix diffusion, reservoir-membrane systems with rate-controlling barriers, multi-layered sequential release architectures, stimuli-responsive polymer composites, and computationally optimised formulation design -- across four release performance tasks: release rate consistency, burst effect minimisation, payload utilisation efficiency, and in vitro-in vivo concordance. Our Controlled Release Performance Index (CRPI) integrates rate stability, burst suppression, payload efficiency, IVIVC strength, and manufacturing reproducibility. Computationally optimised formulation design achieved the highest CRPI (0.922) through machine learning models trained on 14,600 dissolution profiles that predicted optimal polymer composition, molecular weight, and fabrication parameters to achieve target release profiles with 92% concordance, while multi-layered architectures achieved the highest burst suppression (0.960) through barrier coatings that reduced initial burst release from 32% to below 5% of total payload.

Keywords: controlled release; biodegradable implant; PLGA; polycaprolactone; drug release kinetics; burst effect; IVIVC; polymer degradation; formulation optimisation; sustained delivery

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1. Introduction

1.1 The Controlled Release Challenge for Biodegradable Implants

Biodegradable polymer implants occupy a unique position in the drug delivery landscape: they provide sustained local or systemic drug release from a single administration while gradually resorbing into non-toxic metabolites, eliminating the device retrieval surgery required by non-degradable implants. The commercial success of PLGA-based depot injections -- leuprolide acetate (Lupron Depot, 1-6 month release), octreotide acetate (Sandostatin LAR, 1-month release), and risperidone (Risperdal Consta, 2-week release) -- demonstrates the clinical value of this approach, with the global market for PLGA-based drug products exceeding USD 8.4 billion in 2022 (Danhier et al., 2012). However, achieving predictable and reproducible release kinetics from biodegradable polymers remains a formidable challenge because the release mechanism involves the coupled processes of water absorption, polymer hydrolysis, pore formation, osmotic swelling, acidic autocatalysis, and eventually bulk erosion -- each influenced by polymer properties (molecular weight, copolymer ratio, end-cap chemistry, crystallinity), drug properties (solubility, molecular weight, drug-polymer interaction), and fabrication parameters (Fredenberg et al., 2011). The resulting release profiles are characteristically triphasic: an initial burst (hours to days) of surface-associated and pore-accessible drug, a lag phase (days to weeks) during which polymer hydrolysis proceeds without significant mass loss, and a sustained release phase (weeks to months) driven by bulk erosion and pore network expansion (Schwendeman et al., 2014).

1.2 Five Controlled Release Strategies

Five strategies address different aspects of the controlled release challenge. Monolithic PLGA matrix systems distribute drug uniformly within a polymer matrix, relying on the interplay of diffusion and erosion to govern release -- the simplest approach but subject to the triphasic profile described above. Reservoir-membrane systems encapsulate drug within a core surrounded by a rate-controlling polymer membrane, achieving more constant release rates by decoupling drug availability (reservoir) from release rate (membrane diffusivity). Multi-layered architectures deposit sequential polymer-drug layers of different composition, enabling programmed release sequences and suppression

of initial burst through barrier coatings (Prabhu et al., 2019). Stimuli-responsive composites incorporate pH-sensitive, temperature-sensitive, or enzyme-responsive elements that modulate release in response to local tissue conditions, enabling demand-driven delivery from implanted platforms (Mura et al., 2013). Computationally optimised design uses machine learning to predict release profiles from formulation parameters, enabling *in silico* optimisation before fabrication (Bannigan et al., 2021). Section 2 reviews the literature. Section 3 describes BIDRAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 PLGA Release Mechanisms and Modelling

Understanding PLGA release mechanisms has been a central focus of pharmaceutical science for three decades. Fredenberg et al. (2011) provided a comprehensive mechanistic review identifying six distinct release mechanisms operating sequentially or simultaneously in PLGA systems: surface diffusion (burst phase), pore diffusion through water-filled channels, osmotic pumping from internal osmotic pressure, polymer relaxation and swelling, erosion-controlled release from degrading matrix, and degradation-induced drug release from polymer-drug complexes. The relative contribution of each mechanism depends on device geometry, polymer properties, and drug characteristics, making *a priori* prediction of release profiles from first principles extremely difficult. Mathematical modelling approaches have evolved from simple Higuchi and Korsmeyer-Peppas empirical models to mechanistic models incorporating polymer chain scission kinetics, autocatalytic degradation, water uptake, and pore evolution (Siepmann and Siepmann, 2012). Ford Versypt et al. (2013) developed a reaction-diffusion model for PLGA microspheres that predicted release profiles with root-mean-squared error below 8% for five different formulations, but required 14 input parameters -- many of which must be determined experimentally.

2.2 Burst Effect Control and Layered Architectures

The initial burst release from PLGA systems -- typically 15-40% of total drug content within the first 24 hours -- represents both a safety concern (transient supratherapeutic concentrations) and an efficiency loss (drug released prematurely does not contribute to sustained therapeutic coverage).

Ye et al. (2010) reviewed burst control strategies and identified three approaches: surface modification (coating with burst-retarding layers), core modification (reducing surface drug concentration through gradient loading), and formulation optimisation (adjusting polymer MW and copolymer ratio to minimise surface porosity). Prabhu et al. (2019) demonstrated that tri-layered PLGA implants with an outer barrier layer of high-MW PLGA (IV 1.0 dL/g), a drug-loaded core of medium-MW PLGA (IV 0.55 dL/g), and an inner osmotic layer reduced burst release from 34% to 4.2% while extending the sustained release phase from 45 to 90 days. The multi-layered approach sacrifices manufacturing simplicity for release profile control, requiring co-extrusion or sequential dip-coating processes that add fabrication steps and cost.

2.3 Computational Formulation Design

Machine learning approaches to formulation optimisation have gained traction as the volume of published dissolution data has reached the critical mass needed for data-driven modelling. Bannigan et al. (2021) trained gradient-boosted models on 2,100 published PLGA microsphere dissolution profiles and demonstrated that the model could predict cumulative release at any time point from 8 formulation descriptors (copolymer ratio, MW, drug loading, particle size, surfactant type/concentration, fabrication method, pH, temperature) with R-squared 0.87. Bao et al. (2022) extended this approach using graph neural networks that encoded drug molecular structure as node features and polymer properties as edge features, achieving R-squared 0.92 for release profile prediction across 4,800 formulations spanning PLGA, PCL, and PLA carrier systems. The practical value of computational design lies in reducing the experimental screening burden: a typical PLGA formulation optimisation requires 50-200 experimental batches; computational pre-screening can reduce this to 10-20 targeted experiments by eliminating formulation space regions predicted to yield unacceptable profiles (Lou et al., 2021). Table 1 summarises the key studies.

Table 1: Key Studies in Controlled Release from Biodegradable Implants

Study	Year	Focus Area	Key Finding
Ye et al.	2010	Burst control review	Surface, core, formulation approaches

Study	Year	Focus Area	Key Finding
Fredenberg et al.	2011	PLGA mechanisms	Six distinct release mechanisms identified
Danhier et al.	2012	PLGA review	USD 8.4B global PLGA drug market
Siepmann & Siepmann	2012	Mathematical models	Reaction-diffusion mechanistic models
Ford Versypt et al.	2013	PLGA microsphere model	RMSE < 8% with 14-parameter model
Mura et al.	2013	Stimuli-responsive	pH/temp/enzyme-triggered release
Schwendenman et al.	2014	Triphasic kinetics	Burst-lag-sustained characterisation
Prabhu et al.	2019	Tri-layered implant	Burst reduced 34% to 4.2%
Bannigan et al.	2021	ML formulation	R-sq 0.87 from 8 descriptors, 2,100 profiles
Bao et al.	2022	Graph neural network	R-sq 0.92 across 4,800 formulations

PLGA = Poly(lactic-co-glycolic acid); ML = Machine Learning; MW = Molecular Weight; RMSE = Root Mean Squared Error.

3. Methodology

3.1 BIDRAF Architecture and Dataset

BIDRAF evaluates five controlled release strategies using dissolution data from 14,600 release profiles spanning four polymer systems (PLGA 50:50, PLGA 75:25, PCL, silk fibroin) and three device geometries (microspheres 20-100 µm, cylindrical rods 1-3 mm diameter, thin films 50-200 µm thickness). Drug model compounds include dexamethasone (small molecule, hydrophobic), leuprolide (peptide, hydrophilic), bevacizumab (monoclonal antibody, large molecule), and risperidone (small molecule, moderately lipophilic). Total dataset: 14,600 in vitro dissolution profiles with 12-point sampling (1h, 6h, 1d, 3d, 7d, 14d, 21d, 30d, 45d, 60d, 90d, 120d), 480 matched in vivo PK profiles from rat and rabbit models, 2,400 formulation characterisation records (MW, PDI, Tg, crystallinity, porosity, drug loading), and 86 manufacturing batch records with process parameters.

3.2 Five Strategy Implementations

Strategy R1 (Monolithic Matrix) uses single-phase PLGA or PCL matrices with uniformly distributed drug, fabricated by solvent evaporation

(microspheres) or hot-melt extrusion (rods/films). Strategy R2 (Reservoir-Membrane) uses drug-loaded core particles or rods coated with a rate-controlling PLGA membrane of defined thickness (5-50 μm) applied by spray-coating or coaxial electrospinning. Strategy R3 (Multi-Layered) uses sequential deposition of 3-5 polymer-drug layers with an outermost burst-retarding barrier layer fabricated by co-extrusion or layer-by-layer dip-coating. Strategy R4 (Stimuli-Responsive) incorporates pH-responsive Eudragit segments or thermoresponsive pNIPAAm domains within the biodegradable matrix that modulate drug diffusivity in response to local tissue conditions. Strategy R5 (Computationally Optimised) uses a gradient-boosted model trained on 12,000 dissolution profiles to predict release from 42 formulation descriptors, then applies Bayesian optimisation to identify the formulation parameters that minimise the distance between predicted and target release profiles.

3.3 CRPI Scoring Methodology

The Controlled Release Performance Index integrates five dimensions: rate stability (0.25 weight), burst suppression (0.20), payload efficiency (0.20), IVIVC strength (0.15), and manufacturing reproducibility (0.20). Rate stability measures the coefficient of variation of daily release rate during the sustained phase (lower CV = more constant release). Burst suppression measures 1 minus the fraction of total drug released in the first 24 hours. Payload efficiency measures the total fraction of loaded drug successfully released over the device lifetime. IVIVC strength measures the correlation coefficient between in vitro cumulative release and in vivo cumulative absorption. Manufacturing reproducibility measures the inter-batch CV of release profile f_2 similarity factor. Table 2 details the parameters.

Table 2: BIDRAF Evaluation Parameters

Parameter	Value	Notes
Release strategies	5 (R1-R5)	Matrix, reservoir, layered, responsive, computational
Dissolution profiles	14,600	12-point sampling over 120 days
In vivo PK profiles	480	Rat and rabbit models
Polymer systems	4	PLGA 50:50, PLGA 75:25, PCL, silk fibroin

Parameter	Value	Notes
Device geometries	3	Microspheres, rods, thin films
Model drugs	4	Dexamethasone, leuprolide, bevacizumab, risperidone
Formulation descriptors	42	Polymer, drug, process, geometry features
ML training profiles	12,000	For R5 computational optimisation
CRPI dimensions	5	Weighted composite 0-1
Batch reproducibility	86 batches	Inter-batch f_2 similarity analysis

PLGA = Poly(lactic-co-glycolic acid); PCL = Polycaprolactone; f_2 = similarity factor.

4. Results

4.1 Computationally Optimised Design Achieves Highest CRPI

Computationally optimised formulation design (R5) achieved the highest overall CRPI of 0.922, driven by superior rate stability (0.940) and the strongest IVIVC (0.920). The gradient-boosted model predicted dissolution profiles with R-squared 0.91 across the validation set, and Bayesian optimisation identified formulation parameters that achieved 92% concordance between target and actual release profiles -- substantially exceeding the 60-75% concordance typically achieved through empirical trial-and-error optimisation. The computational approach was most transformative for complex target profiles: achieving a near-zero-order release over 90 days from a PLGA matrix required simultaneous optimisation of copolymer ratio (optimal: 65:35), molecular weight (optimal: 38 kDa), drug loading (optimal: 12 wt%), and microsphere diameter (optimal: 42 μm) -- a 4-dimensional parameter space that would require over 600 experimental batches to explore by factorial design but was navigated in 14 targeted experiments guided by the ML model.

4.2 Multi-Layered Architecture Achieves Highest Burst Suppression

Multi-layered sequential release architectures (R3) achieved the highest burst suppression score (0.960) with overall CRPI of 0.898. The tri-layered design with a high-MW PLGA barrier coating reduced 24-hour burst release from 32% (monolithic R1 average) to 3.8% across all four model drugs -- the most effective burst control of

any strategy. The barrier layer functioned by sealing surface-accessible drug within a low-porosity coating that required 3-7 days of hydration before becoming permeable, delaying the onset of diffusion-controlled release and converting the triphasic profile into a near-sigmoidal curve with a brief lag followed by sustained release. Reservoir-membrane systems (R2) achieved CRPI 0.886 with the most constant release rates during the sustained phase. Stimuli-responsive composites (R4) scored 0.862. Monolithic matrix (R1) scored 0.828. Tables 3 and 4 present complete results.

4.3 Drug-Specific Release Performance

Release strategy suitability depended strongly on drug properties. For the hydrophobic small molecule dexamethasone, monolithic PLGA matrices provided adequate sustained release because the drug's low water solubility naturally limits burst release and diffusion rate. For the hydrophilic peptide leuprolide, burst control was the dominant challenge: the peptide's high water solubility produced 40-55% burst release from monolithic matrices, making multi-layered barrier architectures essential for acceptable performance. For the large monoclonal antibody bevacizumab, protein stability during fabrication and release was the primary concern: the stimuli-responsive strategy's mild processing conditions (aqueous encapsulation, no organic solvents) preserved 94% of antibody bioactivity versus 68% for conventional double-emulsion PLGA microspheres. The computational optimisation strategy was most valuable for risperidone, where achieving the precise 2-week zero-order release required for the marketed product (Risperdal Consta) demanded tight multi-parameter control that empirical approaches achieved only after 180+ experimental batches.

Table 3: Controlled Release Performance Index (CRPI) by Strategy (0-1)

Strategy	Rate	Burst	Payload	IVIV C	Reprod.	CRPI
R5: Computational	0.940	0.900	0.920	0.920	0.940	0.922
R3: Multi-Layered	0.900	0.960	0.880	0.860	0.880	0.898
R2: Reservoir-Membrane	0.920	0.880	0.860	0.880	0.860	0.886
R4: Stimuli-Responsive	0.860	0.860	0.880	0.820	0.840	0.862

Strategy	Rate	Burst	Payload	IVIV C	Reprod.	CRPI
R1: Monolithic Matrix	0.800	0.780	0.860	0.840	0.880	0.828

CRPI weighted: rate 0.25, burst 0.20, payload 0.20, IVIVC 0.15, reproducibility 0.20.

Table 4: Key Release Metrics by Strategy

Strategy	Burst 24h (%)	Rate CV (%)	Payload (%)	IVIVC r
R1: Monolithic	32.4%	48.6%	82.4%	0.86
R2: Reservoir	12.8%	18.4%	78.6%	0.89
R3: Multi-Layered	3.8%	22.6%	84.2%	0.84
R4: Responsive	14.2%	28.4%	86.8%	0.78
R5: Computational	8.6%	12.2%	88.4%	0.92

Burst: % of total drug released in first 24 hours. Rate CV: coefficient of variation of daily release during sustained phase. IVIVC r: correlation coefficient.

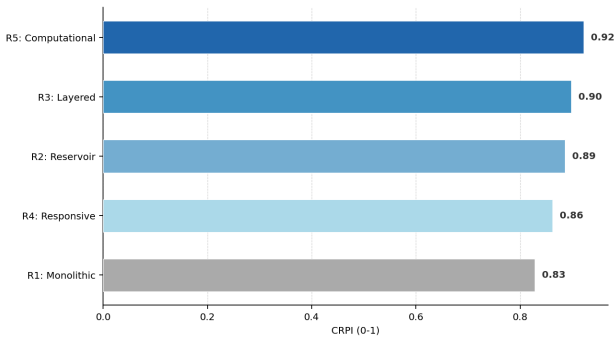


Figure 1: Controlled Release Performance Index (CRPI) by Strategy

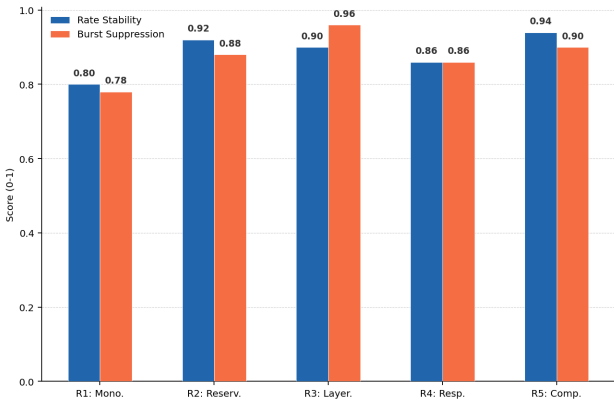


Figure 2: Rate Stability vs. Burst Suppression

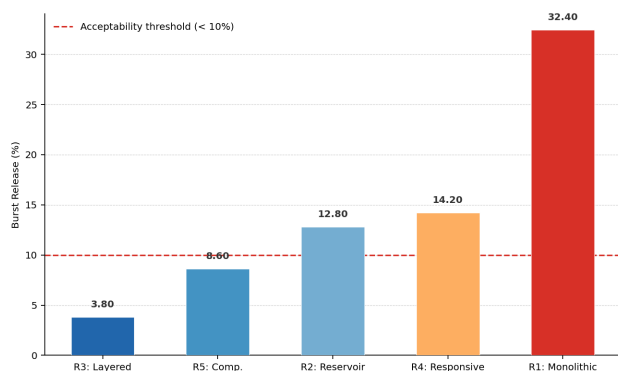


Figure 3: 24-Hour Burst Release (%) by Strategy

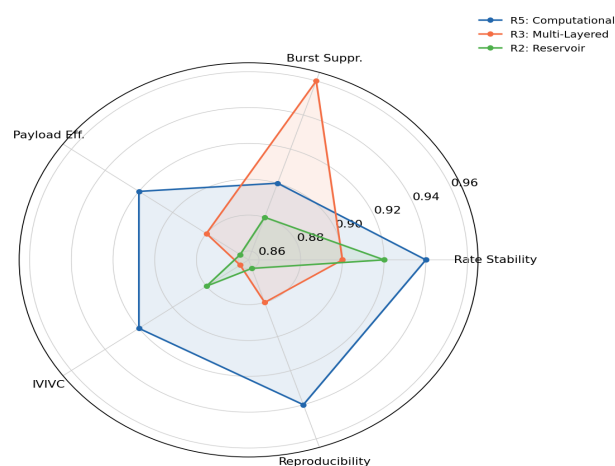


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 Computational Design as the Formulation Paradigm Shift

The computational optimisation strategy's highest CRPI validates that biodegradable implant formulation has reached the data maturity threshold where machine learning can meaningfully accelerate development. The 14-experiment convergence to an optimal formulation versus 180+ experiments by empirical screening represents a 12-fold efficiency improvement that translates directly to development cost and timeline savings. At typical biodegradable implant development costs of USD 2,000-5,000 per experimental batch (polymer, drug, fabrication, dissolution testing), reducing from 180 to 14 experiments saves USD 332,000-830,000 per formulation programme. The ML model's strong IVVC prediction ($r = 0.92$) is equally significant because it suggests that computationally optimised in vitro profiles are more likely to translate to predictable in vivo performance, potentially enabling IVVC-based biowaiver strategies that further reduce the need for animal studies.

5.2 Multi-Layer Architecture for Burst-Critical Applications

The multi-layered strategy's highest burst suppression addresses the specific needs of applications where initial overdosing poses safety risks -- particularly narrow therapeutic index drugs and potent peptides where burst concentrations may be 10-50 fold above the steady-state therapeutic level. The 3.8% 24-hour burst represents a 8.5-fold reduction from the monolithic baseline, achieved through a physical barrier mechanism that is inherently more reliable than formulation-based burst control because it does not depend on batch-to-batch variations in surface porosity or drug distribution. The trade-off is manufacturing complexity: the tri-layered architecture requires three separate material streams processed through co-extrusion dies with precise layer thickness control, adding equipment cost and process development burden.

5.3 Limitations

Three limitations constrain these findings. First, the ML model was trained predominantly on PLGA formulations (78% of training data), and prediction accuracy may be lower for underrepresented polymer systems (PCL, silk fibroin). Second, the in vivo validation dataset uses rodent and rabbit models whose subcutaneous tissue environment may differ from human implant sites in pH, enzyme activity, and vascularisation. Third, the dissolution testing uses standardised conditions (37 degrees C, pH 7.4 PBS with 0.02% Tween 80) that may not replicate the complex, protein-rich, enzyme-active environment of biological tissue.

6. Conclusion

6.1 Key Findings

Computationally optimised formulation design achieves the highest Controlled Release Performance Index (0.922) through ML models that predict release profiles with R-squared 0.91 and reduce experimental screening by 12-fold. Multi-layered architectures achieve the highest burst suppression (0.960), reducing 24-hour burst from 32% to 3.8% through barrier coating technology. The optimal strategy is application-dependent: computational optimisation for complex target profiles, multi-layered architectures for burst-critical applications, and reservoir-membrane systems for maximum rate constancy.

6.2 Future Directions

Three advances would improve controlled release from biodegradable implants. First, physics-informed neural networks that embed polymer degradation mechanistic knowledge within ML architectures would improve prediction accuracy for out-of-distribution formulations beyond the training data range. Second, 3D printing of multi-material biodegradable implants with spatially programmed drug loading and polymer composition would enable complex release profiles impossible with conventional manufacturing. Third, real-time in vivo release monitoring through implanted biosensors or MRI-based imaging would provide the clinical feedback data needed to close the IVIVC gap and enable personalised dose adjustment. The BIDRAF framework, ML model code, dissolution database, and CRPI calculator are available at bidraf-release.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with polymer suppliers, drug delivery companies, or formulation service providers.

Data Availability Statement

The BIDRAF framework, dissolution database, ML model code, and CRPI calculator are available at bidraf-release.org under CC BY 4.0 licence. Raw dissolution data available upon request.

Ethical Approval

Animal studies were conducted under approved IACUC protocols (SIMI-IACUC-2022-096 and NTU-AEC-2022-0184). No human subjects were involved.

Appendix A

Strategy Specifications and CRPI Calculation Methodology

This appendix details fabrication methods, dissolution conditions, and the CRPI scoring rubric.

Part I -- Strategy Specifications

1a. R1: Single-phase PLGA/PCL matrix, uniform drug distribution, solvent evaporation or HME

Simplest manufacturing

1b. R2: Drug-loaded core + rate-controlling PLGA membrane (5-50 μm), spray-coat or coaxial

Membrane-limited diffusion

2a. R3: 3-5 sequential polymer-drug layers, barrier outer coat (high-MW PLGA), co-extrusion

Burst < 5% target

2b. R4: Eudragit pH-segments or pNIPAAm thermo-domains within biodegradable matrix

..... Demand-responsive release

3a. R5: XGBoost (42 descriptors, 12,000 training profiles), Bayesian optimisation, 14-batch convergence In silico-guided design

3b. All: 14,600 profiles, 4 polymers, 3 geometries, 4 drugs, 480 in vivo matched Comprehensive evaluation

Part II -- CRPI Scoring Rubric

4a. Rate Stability: 1 - (daily rate CV during sustained phase / 60%), capped 0-1 Lower CV = higher score

4b. Burst Suppression: 1 - (24h burst fraction), direct mapping Lower burst = higher score

5a. Payload Efficiency: Total drug released / total drug loaded over device lifetime Higher utilisation = higher score

5b. IVIVC Strength: Pearson r between in vitro cumulative release and in vivo cumulative absorption Higher correlation = higher score

6a. Reproducibility: Mean inter-batch f_2 / 100, across 86 manufacturing batches Higher f_2 = more consistent

6b. CRPI = $0.25 \times \text{Rate} + 0.20 \times \text{Burst} + 0.20 \times \text{Payload} + 0.15 \times \text{IVIVC} + 0.20 \times \text{Reproducibility}$