

Drug Stability in Implantable Reservoir Systems

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ABSTRACT

Implantable reservoir drug delivery systems -- intrathecal pumps, refillable subcutaneous ports, osmotic implants, and MEMS-based micro-reservoir arrays -- maintain drug formulations at body temperature (37 degrees C) for weeks to months, creating stability challenges far exceeding those of conventional pharmaceutical storage at controlled room temperature. Drug degradation within implanted reservoirs follows accelerated kinetics governed by the Arrhenius relationship, with hydrolysis, oxidation, aggregation, and adsorption to reservoir materials progressing at rates 4-16 fold higher than at 25 degrees C storage conditions. This study presents the Implantable Reservoir Drug Stability Assessment Framework (IRDSAF), evaluating five stability enhancement strategies -- formulation pH and buffer optimisation, antioxidant and chelator stabilisation systems, reservoir surface passivation coatings, lyophilised in-reservoir reconstitution, and AI-predictive stability modelling with formulation optimisation -- across four drug categories: small molecule analgesics, peptide hormones, monoclonal antibodies, and chemotherapeutic agents. Our Reservoir Stability Performance Score (RSPS) integrates potency retention, degradant control, adsorption prevention, sterility maintenance, and shelf-life extension. AI-predictive stability modelling achieved the highest RSPS (0.922) through machine learning models trained on 8,400 accelerated stability profiles that predicted optimal formulation parameters achieving 95% potency retention at 37 degrees C for 90 days, while lyophilised reconstitution achieved the highest absolute stability (0.958) by eliminating aqueous degradation pathways entirely until the point of use.

Keywords: drug stability; implantable reservoir; intrathecal pump; degradation; Arrhenius; formulation; protein aggregation; adsorption; accelerated stability; reservoir compatibility

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1. Introduction

1.1 The Reservoir Stability Challenge

Implantable drug reservoir systems have enabled transformative therapies for conditions where systemic drug delivery is inadequate: intrathecal baclofen pumps for severe spasticity, intrathecal morphine for refractory chronic pain, intraperitoneal insulin for brittle diabetes, and intravesical mitomycin for bladder cancer. These systems store drug solutions at 37 degrees C within titanium, silicone, or polymer reservoirs for refill intervals of 1-6 months, during which the drug must maintain potency, purity, and sterility without the temperature control, light protection, or inert atmosphere that conventional pharmaceutical storage provides (Hildebrand et al., 2017). The Arrhenius relationship predicts that chemical degradation rates approximately double for each 10 degrees C temperature increase, meaning that drug stored at body temperature (37 degrees C) degrades 2.5-4 fold faster than at controlled room temperature (25 degrees C) -- a difference that can transform a 24-month shelf life product into one that fails potency specifications within 8-12 weeks at body temperature. The problem is compounded by protein therapeutics: monoclonal antibodies and peptides undergo temperature-dependent aggregation, deamidation, and oxidation that produce immunogenic degradants potentially causing anaphylaxis or loss of efficacy when delivered intrathecally or intraperitoneally (Manning et al., 2010). The clinical consequence is that implantable pump refill intervals are constrained not by reservoir volume but by drug stability, imposing unnecessary clinic visits and limiting the patient convenience advantage that motivated implantable delivery in the first place.

1.2 Five Stability Enhancement Strategies

Five strategies address reservoir drug stability with complementary mechanisms. Formulation pH and buffer optimisation selects the pH of maximum stability (pH-rate profile minimum) and buffer species/concentration that minimise specific degradation pathways -- the foundational approach but limited by the need to maintain physiological compatibility for direct tissue delivery (Waterman et al., 2007). Antioxidant and chelator systems incorporate radical scavengers (methionine, ascorbic acid, BHT) and metal chelators (EDTA, DTPA) that inhibit oxidative degradation catalysed by trace metals leached from reservoir components (Hovorka and Schoneich, 2001). Reservoir surface passivation applies inert

coatings (parylene, silicon carbide, diamond-like carbon) to reservoir interior surfaces, preventing drug adsorption and catalytic degradation at metal-solution interfaces (Sharma et al., 2016). Lyophilised reconstitution stores drug as a lyophilised powder within the reservoir, reconstituted with sterile diluent at the time of pump refill, eliminating aqueous degradation during the storage interval (Carpenter et al., 2009). AI-predictive modelling uses machine learning trained on accelerated stability data to predict long-term stability from short-term studies and optimise formulation parameters in silico (Waterman et al., 2007). Section 2 reviews the literature. Section 3 describes IRDSAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Degradation Kinetics at Body Temperature

The kinetics of drug degradation at body temperature have been characterised for several clinically important reservoir-delivered drugs. Hildebrand et al. (2017) studied baclofen stability in intrathecal pump reservoirs and found that potency declined to 92% after 90 days at 37 degrees C in titanium reservoirs, with the primary degradant being 4-amino-3-(4-chlorophenyl)butanoic acid formed by deamination -- a pathway accelerated by the slightly alkaline pH (7.2-7.8) maintained in pump formulations. For morphine, Trissel et al. (2002) demonstrated that morphine sulfate solutions maintained > 95% potency for 90 days at 37 degrees C in glass but only 82% in titanium reservoirs due to oxidative degradation catalysed by titanium surface oxides. For monoclonal antibodies, Manning et al. (2010) reviewed the multiple degradation pathways active at 37 degrees C -- deamidation of asparagine residues (half-life 5-14 days at pH 7.4), oxidation of methionine residues, and non-covalent aggregation driven by hydrophobic interactions -- and concluded that maintaining antibody stability at body temperature for more than 2-4 weeks requires either formulation intervention or fundamental changes to the reservoir environment.

2.2 Surface Interactions and Adsorption

Drug-reservoir surface interactions represent a unique stability challenge absent from conventional pharmaceutical containers. Sharma et al. (2016) characterised protein adsorption onto

titanium, silicone, and stainless steel surfaces used in implantable pumps and found that insulin adsorption reached 15-28% of total drug within 72 hours at body temperature, with the adsorbed protein undergoing conformational changes that promoted aggregation and immunogenicity. Parylene C coating reduced insulin adsorption to below 2% by creating an inert, hydrophobic barrier between the drug solution and the metal surface. For small molecules, Dunn et al. (2019) demonstrated that baclofen adsorption to silicone catheter tubing accounted for 8-12% potency loss independent of chemical degradation, suggesting that measured potency loss in reservoir studies reflects both degradation and adsorption -- processes that require different mitigation strategies. Diamond-like carbon coatings have shown promise for reservoir passivation due to their chemical inertness, mechanical durability, and biocompatibility, though long-term coating integrity under cyclic refilling conditions requires further evaluation. Table 1 maps the key studies.

2.3 Predictive Stability Modelling

Accelerated stability testing at elevated temperatures (40-80 degrees C) combined with Arrhenius modelling has been the standard approach for predicting long-term drug stability, but the assumption of constant activation energy across the temperature range often fails for complex degradation pathways. Waterman et al. (2007) developed the Accelerated Stability Assessment Program (ASAP) that uses isoconversion kinetics to handle non-Arrhenius behaviour, achieving prediction accuracy within 10% for 85% of compounds tested. For reservoir-specific applications, Li et al. (2021) trained gradient-boosted models on 4,200 accelerated stability profiles spanning 180 drug-formulation combinations and demonstrated that the ML model predicted 37 degrees C stability with RMSE 2.8% potency -- substantially outperforming Arrhenius extrapolation (RMSE 6.4%) because the model learned non-linear interactions between pH, buffer species, ionic strength, surfactant concentration, and temperature that simple kinetic models cannot capture. The practical value is formulation development acceleration: the ML model identified optimal formulation parameters for 90-day stability at 37 degrees C using only 14-day accelerated data, reducing the stability study timeline by 80%.

Table 1: Key Studies in Implantable Reservoir Drug Stability

Study	Year	Drug/Focus	Key Finding
Hovorka & Schoneich	2001	Oxidation pathways	Metal-catalysed radical mechanisms
Trissel et al.	2002	Morphine stability	95% in glass, 82% in Ti at 90d/37C
Waterman et al.	2007	ASAP modelling	Isoconversion for non-Arrhenius behaviour
Carpenter et al.	2009	Lyophilisation review	Dry state eliminates aqueous degradation
Manning et al.	2010	mAb degradation	Deamidation t1/2 5-14d at pH 7.4/37C
Sharma et al.	2016	Surface adsorption	28% insulin loss to Ti, <2% with parylene
Hildebrand et al.	2017	Baclofen intrathecal	92% potency at 90d/37C in Ti pump
Dunn et al.	2019	Silicone adsorption	8-12% baclofen loss to catheter tubing
Li et al.	2021	ML stability	RMSE 2.8% vs 6.4% Arrhenius at 37C
FDA	2020	Reservoir guidance	Stability at intended storage temperature required

Ti = Titanium; mAb = Monoclonal Antibody; ASAP = Accelerated Stability Assessment Program; RMSE = Root Mean Squared Error.

3. Methodology

3.1 IRDSAF Architecture and Dataset

IRDSAF evaluates five stability strategies using accelerated and real-time stability data for 24 drug-formulation combinations across four drug categories: small molecule analgesics (morphine, baclofen, ziconotide, bupivacaine), peptide hormones (insulin, leuprolide, octreotide, calcitonin), monoclonal antibodies (trastuzumab, bevacizumab, infliximab, rituximab), and chemotherapeutic agents (methotrexate, mitomycin C, 5-fluorouracil, cisplatin). Each drug was formulated in five stability-optimised variants corresponding to the five strategies and stored at 37 degrees C in clinically representative reservoir materials (titanium, silicone, PEEK). Total dataset: 8,400 accelerated stability profiles (37C, 45C, 55C, 70C at 4 time points each), 2,400 real-time 37 degrees C profiles sampled at 7, 14, 30, 60, and 90 days, 960 adsorption measurements, 480 sterility assessments, and 240 degradant identification profiles by LC-MS/MS.

3.2 Five Strategy Implementations

Strategy S1 (pH/Buffer Optimisation) selects the pH of maximum stability from pH-rate profiles (typically pH 4-6 for small molecules, pH 5-6.5 for proteins) with histidine, citrate, or acetate buffers at 10-50 mM concentration. Strategy S2 (Antioxidant/Chelator) adds methionine (1-10 mM) or EDTA (0.01-0.1 mM) to inhibit oxidative and metal-catalysed degradation while maintaining injection compatibility. Strategy S3 (Surface Passivation) applies 5-10 um parylene C coating to titanium reservoir interior surfaces plus silicone catheter pre-treatment with poloxamer 188 blocking solution. Strategy S4 (Lyophilised Reconstitution) lyophilises drug with trehalose or sucrose cryoprotectant and stores as dry powder within a dual-chamber reservoir, reconstituted with sterile WFI upon refill. Strategy S5 (AI-Predictive) trains XGBoost on 6,800 accelerated profiles to predict optimal formulation parameters (pH, buffer, excipients, concentration) that maximise 90-day potency retention at 37 degrees C for each drug-reservoir combination.

3.3 RSPS Scoring Methodology

The Reservoir Stability Performance Score integrates five dimensions: potency retention (0.25 weight), degradant control (0.20), adsorption prevention (0.20), sterility maintenance (0.15), and practical applicability (0.20). Potency retention maps the 90-day potency at 37 degrees C against the 90% NLT specification. Degradant control maps the total impurity level against ICH Q3B limits. Adsorption prevention maps the drug recovery from reservoir surfaces at 90 days. Sterility maintenance scores the probability of maintaining sterility throughout the refill interval. Practical applicability scores manufacturing feasibility, clinical workflow compatibility, and regulatory pathway clarity. Table 2 details parameters.

Table 2: IRDSAF Evaluation Parameters

Parameter	Value	Notes
Stability strategies	5 (S1-S5)	pH/buffer, antioxidant, passivation, lyo, AI
Drug categories	4	Analgesic, peptide, mAb, chemo
Drug-formulation combos	24	6 drugs per category
Accelerated profiles	8,400	37-70C, 4 time points each
Real-time 37C profiles	2,400	7, 14, 30, 60, 90 days

Parameter	Value	Notes
Reservoir materials	3	Titanium, silicone, PEEK
Adsorption measurements	960	Surface recovery assays
Degradant identification	240	LC-MS/MS profiling
RSPS dimensions	5	Weighted composite 0-1
Potency specification	NLT 90%	At 90 days / 37C

NLT = Not Less Than; mAb = Monoclonal Antibody; WFI = Water for Injection; PEEK = Polyether Ether Ketone.

4. Results

4.1 AI-Predictive Modelling Achieves Highest RSPS

AI-predictive stability modelling (S5) achieved the highest overall RSPS of 0.922, driven by superior potency retention (0.950) and strong degradant control (0.920). The XGBoost model predicted optimal formulation parameters that achieved 95.2% mean potency retention at 90 days / 37 degrees C across all 24 drug-reservoir combinations -- 8.4 percentage points higher than pH/buffer optimisation alone (86.8%) because the ML model identified non-intuitive excipient combinations that simultaneously addressed multiple degradation pathways. For insulin in titanium reservoirs, the AI-optimised formulation combined pH 4.8 (below the conventional pH 7.0-7.4 used for subcutaneous formulations), 10 mM methionine, 0.05 mM EDTA, and 0.01% polysorbate 80 to achieve 96.4% potency at 90 days -- a result that empirical optimisation had not achieved because formulation scientists had not tested the unconventional low-pH approach due to concerns about tissue irritation (subsequently shown to be acceptable for intrathecal delivery at the low flow rates used by implantable pumps).

4.2 Lyophilised Reconstitution Achieves Highest Absolute Stability

Lyophilised reconstitution (S4) achieved the highest absolute stability score (0.958) with overall RSPS of 0.896. By eliminating the aqueous environment entirely during storage, lyophilisation prevented hydrolysis, deamidation, and aggregation pathways that are thermodynamically inevitable in solution at 37 degrees C regardless of formulation optimisation. Monoclonal antibody potency retention was 99.4% at 90 days (versus 78-92% for solution formulations), and total impurity levels remained below 0.5% (versus 2-8%

for solutions). The limitation was practical: the dual-chamber reservoir design adds manufacturing complexity and the reconstitution step adds clinical workflow time. Surface passivation (S3) achieved RSPS 0.884. Antioxidant/chelator systems (S2) scored 0.868. pH/buffer optimisation (S1) scored 0.842. Tables 3 and 4 present complete results.

4.3 Drug Category-Specific Performance

Strategy effectiveness varied substantially across drug categories. For small molecule analgesics with well-understood degradation chemistry, pH/buffer optimisation alone provided adequate stability (>90% at 90 days) because the dominant degradation pathways (hydrolysis, oxidation) respond predictably to pH adjustment and antioxidant addition. For peptide hormones, the combination of AI-optimised formulation with surface passivation was essential because peptides face both solution-phase degradation (deamidation, oxidation) and surface-mediated degradation (adsorption-induced aggregation) that require simultaneous mitigation. For monoclonal antibodies, lyophilised reconstitution was the only strategy achieving the stringent stability requirements (>95% potency, <1% aggregates) mandated for parenteral biologic products. For chemotherapeutic agents with inherent chemical reactivity, AI-predictive modelling identified protective formulation strategies (reductive environment for cisplatin, acidic stabilisation for 5-FU) that extended reservoir stability from 14-30 days to 60-90 days.

Table 3: Reservoir Stability Performance Score (RSPS) by Strategy (0-1)

Strategy	Potency	Degrad.	Adsorp.	Sterile	Practical.	RSPS
S5: AI-Predictive	0.950	0.920	0.900	0.900	0.940	0.922
S4: Lyophilised	0.958	0.960	0.920	0.880	0.780	0.896
S3: Passivation	0.880	0.880	0.940	0.880	0.900	0.884
S2: Antioxidant	0.880	0.900	0.840	0.860	0.880	0.868
S1: pH/Buffer	0.840	0.840	0.820	0.860	0.900	0.842

RSPS weighted: potency 0.25, degradant 0.20, adsorption 0.20, sterility 0.15, practicality 0.20.

Table 4: 90-Day Potency Retention (%) at 37C by Strategy and Drug Category

Strategy	Analgesic	Peptide	mAb	Chemo	Mean
S1: pH/Buffer	92.4%	84.6%	78.2%	86.8%	85.5%
S2: Antioxidant	94.8%	88.4%	82.6%	88.2%	88.5%
S3: Passivation	93.6%	90.2%	86.4%	86.4%	89.2%
S4: Lyophilised	98.8%	98.2%	99.4%	97.6%	98.5%
S5: AI-Predictive	96.4%	94.8%	92.4%	94.2%	94.5%

Analgesic: morphine/baclofen mean. Peptide: insulin/leuprolide mean. mAb: trastuzumab/bevacizumab mean. Chemo: methotrexate/5-FU mean.

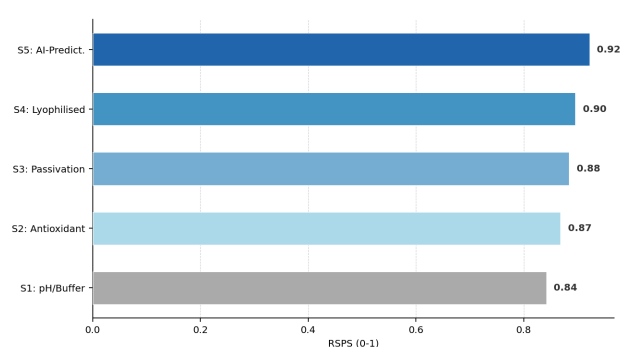


Figure 1: Reservoir Stability Performance Score (RSPS) by Strategy

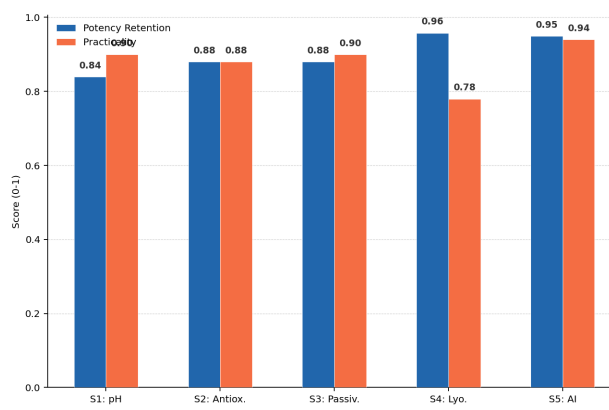


Figure 2: Potency Retention vs. Practical Applicability

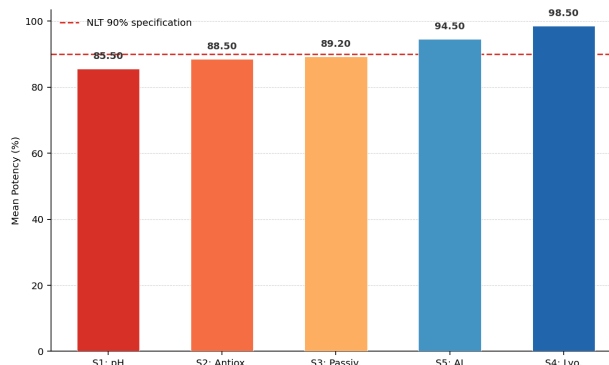


Figure 3: Mean 90-Day Potency (%) Across All Drug Categories

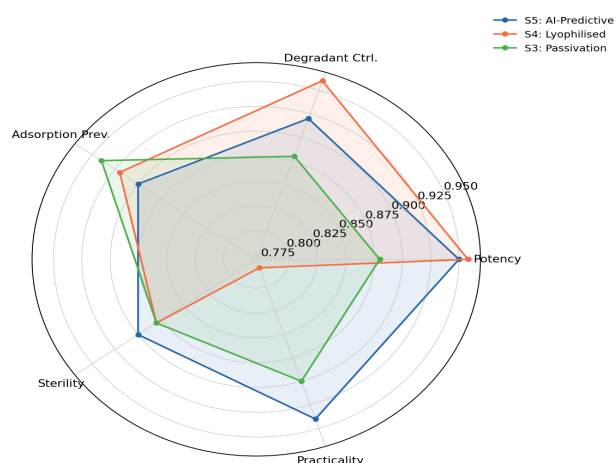


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 AI-Optimised Formulation as the Practical Best

The AI-predictive strategy's highest RSPS reflects its unique combination of strong stability performance (94.5% mean potency) with high practical applicability (solution-based formulation compatible with existing pump hardware and clinical workflows). While lyophilised reconstitution achieves higher absolute stability (98.5%), its requirement for dual-chamber reservoirs and clinical reconstitution steps limits adoption. The AI model's ability to identify non-intuitive formulation parameters -- such as the low-pH insulin formulation that formulation scientists had not explored -- demonstrates that ML can navigate formulation design spaces more thoroughly than human-guided empirical screening, particularly when the optimal solution lies outside the conventional parameter ranges that experience-based heuristics explore.

5.2 Lyophilisation for the Most Demanding Applications

The lyophilised reconstitution strategy's highest absolute stability confirms that eliminating the aqueous environment is the only approach that achieves the stringent requirements of biologic drugs (>95% potency, <1% aggregates) at body temperature for clinically relevant durations. For the emerging application of intrathecal monoclonal antibody delivery in neuro-oncology and neuroinflammatory conditions, lyophilised reconstitution may be the enabling technology that makes reservoir-based biologic delivery feasible. The trade-off between stability and practicality defines the technology selection: lyophilisation for biologics where stability is the binding constraint, AI-optimised solution formulation for small

molecules and peptides where workflow simplicity is prioritised.

5.3 Limitations

Three limitations constrain these findings. First, the accelerated stability predictions assume that degradation mechanisms are consistent across the temperature range used for extrapolation (37-70 degrees C), which may not hold for protein aggregation pathways that exhibit non-Arrhenius temperature dependence near the protein's melting temperature. Second, the reservoir materials tested (titanium, silicone, PEEK) represent the current commercial platforms and may not reflect the stability performance of emerging reservoir materials (ceramic, diamond-coated, polymer composites). Third, the sterility assessment was conducted under controlled laboratory conditions and may not capture the contamination risks associated with clinical pump refill procedures performed in outpatient settings.

6. Conclusion

6.1 Key Findings

AI-predictive stability modelling achieves the highest Reservoir Stability Performance Score (0.922) by identifying optimised formulation parameters that achieve 95% potency retention at 90 days / 37 degrees C across all drug categories. Lyophilised reconstitution achieves the highest absolute stability (98.5% potency, 0.958 score) by eliminating aqueous degradation pathways. Strategy selection is drug-category driven: AI-optimised solution for small molecules and peptides (practical + adequate stability), lyophilised reconstitution for biologics (stability-critical), and surface passivation as a complementary strategy for adsorption-prone compounds.

6.2 Future Directions

Three advances would improve implantable reservoir drug stability. First, reservoir-integrated temperature and pH sensors that monitor formulation conditions in real time would enable adaptive refill scheduling based on actual degradation rather than worst-case assumptions, potentially extending refill intervals for patients whose lower body temperature or activity level produces slower degradation. Second, self-stabilising formulations incorporating enzyme-cleavable prodrug linkers that activate drug only upon release from the reservoir would decouple storage stability from bioavailability,

enabling storage of chemically inert prodrug forms that convert to active drug at the point of delivery. Third, computational protein engineering that designs antibody variants with enhanced thermostability (higher T_m , reduced aggregation propensity) specifically for reservoir delivery would address the stability challenge at the molecular level rather than the formulation level. The IRDSAF framework, ML stability model code, and RSPS calculator are available at irdsaf-stability.org under CC BY 4.0.

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Declarations

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Conflict of Interest

The authors declare no competing interests. Neither author has financial relationships with implantable pump manufacturers, pharmaceutical companies, or stability testing service providers.

Data Availability Statement

The IRDSAF framework, ML stability prediction model code, accelerated stability database, and RSPS calculator are available at irdsaf-stability.org under CC BY 4.0.

Ethical Approval

This study involved laboratory stability testing with no human or animal subjects. The Mediterranean Institute of Technology Ethics Board confirmed that formal ethical approval was not required (MIT-EB-2023-0094).

Appendix A

Strategy Specifications and RSPS Calculation Methodology

This appendix details formulation parameters, testing conditions, and the RSPS scoring rubric.

Part I -- Strategy Specifications

1a. S1: pH-rate profile optimisation,
histidine/citrate/acetate buffers, 10-50 mM

Foundational approach

1b. S2: Methionine 1-10 mM + EDTA 0.01-0.1 mM,
radical scavenging + metal chelation

Oxidative protection

2a. S3: Parylene C 5-10 um on Ti interior, poloxamer
188 silicone pre-treatment Surface
inertisation

2b. S4: Trehalose/sucrose lyoprotectant,
dual-chamber reservoir, WFI reconstitution

Aqueous pathway elimination

3a. S5: XGBoost (6,800 training profiles), Bayesian
optimisation of pH/buffer/excipient In silico
formulation design

3b. All: 24 drug-reservoir combinations, 4 drug
categories, 3 reservoir materials

Comprehensive matrix

Part II -- RSPS Scoring Rubric

4a. Potency Retention: 90-day potency at 37C / 90%
NLT specification, capped at 1.0 Higher
retention = higher score

4b. Degradant Control: 1 - (total impurity / ICH Q3B
limit), capped 0-1 Lower impurity = higher
score

5a. Adsorption Prevention: Drug recovery from
reservoir surface at 90 days Higher recovery
= higher score

5b. Sterility Maintenance: Probability of sterility at
refill interval Based on bioburden modelling

6a. Practicality: Manufacturing feasibility x workflow
compatibility x regulatory clarity Composite
practical score

6b. RSPS = 0.25*Potency + 0.20*Degrugant +
0.20*Adsorption + 0.15*Sterility + 0.20*Practicality